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(54) Use of serotonin 5-HT1F agonists for the prevention of migraine

(57) This invention provides methods for the prevention of migraine which comprises administering to a mammal in need thereof a serotonin 5-HT_{1F} agonist

EP 0 832 650 A2

Description

The diverse physiological activity exhibited by the neurotransmitter serotonin (5-HT) is mediated by at least seven receptor classes 5-HT_1 5-HT_2 5-HT_3 5-HT_4 5-HT_5, 5-HT_6 and 5-HT_7 The most heterogeneous of these classes appears to be 5-HT_1 subclassified as 5-HT_{1A} 5-HT_{1B} 5-HT_{1C} 5-HT_{1D} (Hamon *et al Neuropsychopharmacol*. **3** (5/6), 349-360 (1990)) and 5-HT_{1E} (Leonhardt *et al J Neurochem*. **53**(2) 465-471 (1989)) A human gene which expresses an additional 5-HT_1 subclass 5-HT_{1F} was isolated by Kao and coworkers (*Proc Natl Acad Sci USA*. **90** 408-412 (1993)) This 5-HT_{1F} receptor has been shown to exhibit a pharmacological profile distinct from any serotonergic receptor yet described

Theories regarding the pathophysiology of migraine have been dominated since 1938 by the work of Graham and Wolff (*Arch Neurol Psychiatry*, **39**, 737-63 (1938)) They proposed that the cause of migraine headache pain is vasodilatation of extracranial vessels This view is supported by knowledge that ergot alkaloids and sumatriptan contract cephalic vascular smooth muscle and are effective in the treatment of migraine Sumatriptan is a hydrophilic agonist at 5-HT-1-like receptors and does not cross the blood-brain barrier (Humphrey *et al*, *Ann NY Acad Sci*. **600** 587-600 (1990)) Recently several new series of compounds said to be useful for the treatment of migraine have been described in WO94/03446 WO93/11106 WO92/13856 EP0438230 and WO91/18897 Each of these series of compounds has been developed to optimize the 5-HT_1-like mediated vasoconstrictive activity of sumatriptan Sumatriptan's contraindications coronary vasospasm hypertension and angina however are also products of its vasoconstrictive activity (MacIntyre P D . *et al*, *British Journal of Clinical Pharmacology*, **34**, 541-546 (1992). Chester, A H *et al*, *Cardiovascular Research*, **24** 932-937 (1990) Conner J E *et al*. *European Journal of Pharmacology*, **161** 91-94 (1990))

While this vascular mechanism for migraine has gained wide acceptance there is not total agreement as to its validity Moskowitz has shown for example that the occurrence of migraine headaches is independent of changes in vessel diameter (*Cephalalgia*. **12**, 5-7 (1992)) Furthermore Moskowitz has proposed that currently unknown triggers stimulate trigeminal ganglia which innervate vasculature within cephalic tissue giving rise to release of vasoactive neuropeptides from axons on the vasculature These released neuropeptides then initiate a series of events leading to neurogenic inflammation a consequence of which is pain This neurogenic inflammation is blocked by sumatriptan and ergot alkaloids at a dose similar to that required to treat acute migraine in humans While this blockade of neurogenic protein extravasation is believed to be mediated by 5-HT_{1D} receptors the effective dosages of 5-HT_{1D} selective compounds do not correlate with in vitro binding at the 5-HT_{1D} binding site The lack of correlation suggests that a receptor subtype other than 5-HT_{1D} may mediate the effects of sumatriptan (*Neurology*, **43** (suppl 3) S16-S20 (1993)) In addition it has been reported that α_2, H_3 μ-opioid and somatostatin receptors may also be located on trigeminovascular fibers and may block neurogenic plasma extravasation (Matsubara *et al*, *Eur J Pharmacol*. **224**, 145-150 (1992)) Weinshank *et al* have reported that sumatriptan and several ergot alkaloids have a high affinity for the 5-HT_{1F} receptor, suggesting a role for the 5-HT_{1F} receptor in migraine (WO93/14201)

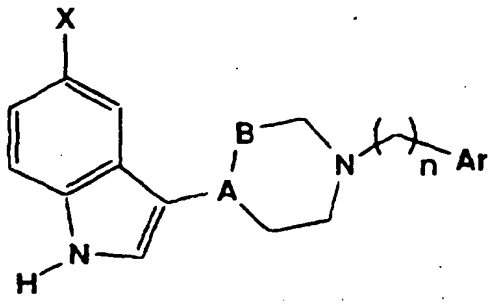
The present invention provides a method for the prevention of migraine and related disorders in mammals, comprising administering an effective amount of a 5-HT_{1F} agonist or a composition exhibiting 5-HT_{1F} agonist activity

The present invention provides a method for the prevention of migraine and associated disorders which relies on a novel mechanism of action By treating a migraineur with a compound or composition which is an agonist at the 5-HT_{1F} receptor, the neurogenic meningeal extravasation which leads to the pain of migraine is inhibited This mechanism is operative in mammals and the preferred mammal is a human

A further embodiment of this invention comprises the administration of a composition which exhibits selective 5-HT_{1F} agonist activity The composition may be composed of one or more agents which individually or together are selective agonists of 5-HT_{1F} receptors relative to other serotonin receptors which produce unwanted effects like vasoconstriction

The term "5-HT_{1F} agonist" as it is used in the description of this invention is taken to mean a full or partial agonist A compound which is a partial agonist at the 5-HT_{1F} receptor must exhibit sufficient agonist activity to inhibit neurogenic meningeal extravasation at an acceptable dose While a partial agonist of any intrinsic activity may be useful for the method of this invention, partial agonists of at least about 50% agonist effect (E_{max}) are preferred and partial agonists of at least about 80% agonist effect (E_{max}) are more preferred Full agonists at the 5-HT_{1F} receptor are most preferred

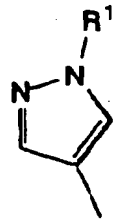
A number of serotonin 5-HT_{1F} agonists are known in the art and are useful for the method of the present invention One such class of compounds are optionally substituted 3-<1 2 3 6-tetrahydro-<1-alkyleneheteroaryl>-4-pyridinyl>-1H-indoles and 3-<1-alkyleneheteroaryl>-4-piperidinyl>-1H-indoles of Formula I



I

in which

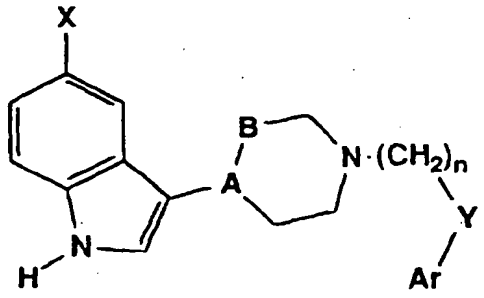
A-B is -CH-CH_2- or -C=CH-
X is H, halo, C_1-C_4 alkoxy, C_1-C_4 alkylthio C_1-C_4 alkyl, benzyloxy hydroxy or carboxamido,
n is 1-4
Ar is pyridinyl pyrrolyl or a structure of Formula II



II

where R^1 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl C_3-C_7 cycloalkylmethyl, benzyl phenyl or substituted phenyl These compounds their synthesis and use as serotonin 5-HT_{1F} agonists are described in U S Patent #5,521,196, issued May 28, 1996 This reference is hereby incorporated by reference in its entirety

An additional class of 5-HT_{1F} agonists are the optionally substituted 3-<1,2,3 6-tetrahydro-<1-alkylenearyl>-4-pyridinyl>-1H-indoles and 3-<1-alkylenearyl>-4-piperidinyl>-1H-indoles of Formula III



III

in which

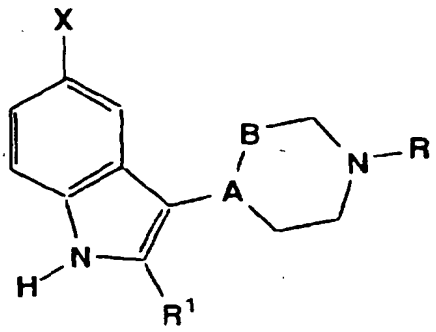
A-B is -CH-CH_2- or -C=CH-,
X is H, halo C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkyl benzyloxy, hydroxy or carboxamido
Y is O, S or a bond

n is 1-4

Ar is 1-naphthyl 2-naphtyl phenyl or phenyl monosubstituted with a substituent selected from the group consisting of halo C_1-C_4 alkoxy C_1-C_4 alkylthio C_1-C_4 alkyl benzyloxy, hydroxy or trifluoromethyl These compounds their synthesis and use as serotonin 5-HT_{1F} agonists are described in U S Patent #5 521 197 issued May 28 1996 This reference is hereby incorporated by reference in its entirety

The compounds of Formulae I and III may be prepared by methods well known to the skilled artisan Briefly an appropriately substituted indole is reacted with an appropriate 1-substituted-4-piperidone in the presence of base to provide the corresponding 3-(1 2 3 6-tetrahydro-pyridin-4-yl)-1H-indole These compounds may be used directly for the method of the invention or reduced to provide the corresponding 3-(piperidin-4-yl)-1H-indoles useful for the method of the invention Compounds prepared in this matter may also serve as substrates for the preparation of other compounds useful for the method of the present invention

A further class of compounds useful for the method of the present invention are 5-substituted-3-(1 2 3 6-tetrahydropyridin-4-yl)-1H-indoles and 5-substituted-3-(piperidin-4-yl)-1H-indoles of Formula IV



IV

in which

A-B is -CH-CH_2- or -C=CH-,
R is H or C_1-C_6 alkyl,
R^1 is H or C_1-C_4 alkyl,
X is -S-R^2 -C(O)R^3 -C(O)NR^4R^{15} -NR^5R^6 -N$R^7SO_2R^8$ -NHC(Q)N$R^{10}R^{11}$ -NHC(O)OR^{12} or -NR^{13}C(O)R^{14}

where

Q is O, or S
R^2 is phenyl substituted phenyl, phenyl(C_1-C_4 alkylene) phenyl(C_1-C_4 alkylene) substituted in the phenyl ring, or pyridinyl
R^3 is C_1-C_6 alkyl, phenyl(C_1-C_4 alkylene), phenyl(C_1-C_4 alkylene) substituted in the phenyl ring, naphthyl, N-methyl-N-methoxyamino heteroaryl, substituted heteroaryl heteroaryl(C_1-C_4 alkyl), or substituted heteroaryl(C_1-C_4 alkyl)
R^4 is heteroaryl substituted heteroaryl heteroaryl(C_1-C_4 alkyl), or substituted heteroaryl(C_1-C_4 alkyl),
R^4 and R^{15} taken together with the nitrogen atom form a pyrrolidine, piperidine substituted piperidine piperazine 4-substituted piperazine morpholine or thiomorpholine ring,
R^5 and R^6 are both trifluoromethanesulfonyl,
R^7 is H or C_1-C_4 alkyl
R^8 is C_1-C_4 alkyl, phenyl, substituted phenyl or di(C_1-C_4 alkyl)amino,
R^{10} and R^{11} are independently selected from the group consisting of C_1-C_6 alkyl C_3-C_6 alkenyl C_3-C_8 cycloalkyl phenyl substituted phenyl, phenyl(C_1-C_4 alkylene) phenyl(C_1-C_4 alkylene) substituted in the phenyl ring, ((C_1-C_4 alkyl or C_1-C_4 alkoxycarbonyl substituted)C_1-C_4 alkyl)phenyl C_1-C_4 alkyl α-substituted with C_1-C_4 alkoxycarbonyl or
R^{10} and R^{11} taken together with the nitrogen atom form a pyrrolidine piperidine, piperazine 4-substituted piperazine morpholine or thiomorpholine ring
R^{12} is C_1-C_6 alkyl C_3-C_6 alkenyl phenyl, substituted phenyl, C_3-C_3 cycloalkyl, C_1-C_4 alkyl ω-substituted with C_1-

C_4 alkoxy
R^{13} is H or C_1-C_4 alkyl
R^{14} is C_1-C_{10} alkyl substituted with up to three substituents selected from the group consisting of hydroxy, C_1-C_4 alkoxy halo aryloxy C_1-C_4 alkoxycarbonyl and heteroaryloxy, C_2-C_{10} alkenyl C_2-C_{10} alkynyl C_3-C_8 cycloalkyl, phenyl substituted phenyl, naphthyl, phenyl(C_1-C_4 alkylene), phenyl(C_1-C_4 alkylene) substituted on the phenyl ring 2-phenylethylen-1-yl diphenylmethyl, benzofused C_4-C_8 cycloalkyl C1-C4 alkylene ω-substituted with C_3-C_6 cycloalkyl or a heterocycle and
R^{15} is H or C_1-C_6 alkyl

The general chemical terms used in the formulae above have their usual meanings For example, the terms "alkyl, alkoxy and alkylthio" include such groups as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 2-pentyl- 3-pentyl- neopentyl, hexyl, heptyl, octyl and the like The term "alkenyl" includes vinyl, allyl 1-buten-4-yl, 2-buten-4-yl 1-penten-5-yl, 2-penten-5-yl, 3-penten-5-yl, 1-hexen-6-yl 2-hexen-6-yl 3-hexen-6-yl 4-hexen-6-yl and the like The term "alkynyl" includes acetylenyl, propynyl, 2-butyn-4-yl 1-butyn-4-yl 1-pentyn-5-yl, 2-pentyn-5-yl and the like The term "acyl" includes for example formyl, acetyl, propanoyl butanoyl, and 2-methylpropanoyl The term "cycloalkyl" includes such groups as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl The term "phenyl(C_1-C_4 alkylene)" includes such groups as benzyl phenethyl, phenpropyl and phenbutyl The term "(C_1-C_4 alkyl)sulfonyl" includes methanesulfonyl, ethanesulfonyl propanesulfonyl, isopropanesulfonyl, butanesulfonyl and the like The term "halo" includes fluoro, chloro bromo and iodo

The term "substituted phenyl" or "phenyl(C_1-C_4 alkylene) substituted in the phenyl ring" is taken to mean the phenyl moiety may be substituted with one substituent selected from the group consisting of halo, C_1-C_4 alkyl, C_1-C_8 alkoxy, C_1-C_4 alkylthio, nitro, cyano, di(C_1-C_4 alkyl)amino trifluoromethyl trifluoromethoxy, phenyl, C_1-C_4 acyl benzoyl or (C_1-C_4 alkyl)sulfonyl, or two to three substituents independently selected from the group consisting of halo nitro, C_1-C_4 alkyl or C_1-C_4 alkoxy

The term "heterocycle" is taken to mean stable aromatic and non-aromatic 5- and 6-membered rings containing from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, said rings being optionally benzofused All of these rings may be substituted with up to three substituents independently selected from the group consisting of halo, C_1-C_4 alkoxy, C_1-C_4 alkyl, cyano nitro, hydroxy,-$S(O)_n$-(C_1-C_4 alkyl) and -$S(O)_n$-phenyl where n is 0, 1 or 2 Non-aromatic rings include, for example, pyrrolidinyl piperidinyl piperazinyl, tetrahydrofuryl, oxazolidinyl, dioxanyl pyranyl and the like Benzofused non-aromatic rings include indolinyl 1 2 3,4-tetrahydroquinolinyl 1,2,3,4-tetrahydroisoquinolinyl and the like Aromatic rings include furyl thienyl, pyridinyl, pyrrolyl N-methylpyrrolyl oxazolyl isoxazolyl, pyrazolyl, imidazolyl, triazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, and the like Benzofused aromatic rings include isoquinolinyl, benzoxazolyl, benzthiazolyl, quinolinyl, benzofuranyl, thionaphthyl, indolyl and the like

The term "heteroaryl" is taken to mean an aromatic or benzofused aromatic heterocycle as defined in the previous paragraph The term "substituted heteroaryl" is taken to mean an aromatic or benzofused aromatic heterocycle as defined in the previous paragraph substituted with up to three substituents independently selected from the group consisting of halo, C_1-C_4 alkoxy, C_1-C_4 alkyl, cyano nitro, hydroxy,-$S(O)_n$-(C_1-C_4 alkyl) and -$S(O)_n$-phenyl where n is 0, 1 or 2 The term "heteroaryl(C_1-C_4 alkyl) is taken to mean a branched or linear alkyl chain of 1 to 4 carbon atoms substituted at some point with an aromatic or benzofused aromatic heterocycle moiety The term "substituted heteroaryl (C_1-C_4 alkyl)" is taken to mean a branched or linear alkyl chain of 1 to 4 carbon atoms substituted at some point with an aromatic or benzofused aromatic heterocycle moiety which is substituted with up to three substituents independently selected from the group consisting of halo, C_1-C_4 alkoxy, C_1-C_4 alkyl, cyano, nitro, hydroxy, -$S(O)_n$-(C_1-C_4 alkyl) and -$S(O)_n$-phenyl where n is 0, 1 or 2

The term "heteroaryloxy" is taken to mean a heteroaryl or substituted heteroaryl group, as defined in the previous paragraph bonded to an oxygen atom

The term "aryloxy" is taken to mean a phenyl or substituted phenyl group bonded to an oxygen atom

The term "4-substituted piperazine" is taken to mean a piperazine ring substituted at the 4-position with a substituent selected from the group consisting of C_1-C_6 alkyl, C_1-C_4 alkoxy substituted C_1-C_6 alkyl phenyl, substituted phenyl, phenyl(C_1-C_4 alkylene), phenyl(C_1-C_4 alkylene) substituted in the phenyl ring, heteroaryl and heteroaryl(C_1-C_4 alkylene)

The term "substituted piperidine" is taken to mean a piperidine ring optionally substituted with a substituent selected from the group consisting of hydroxy, hydroxymethyl, and N N-di(C_1-C_4 alkyl)carboxamido

The term "benzofused C_4-C_8 cycloalkyl" is taken to mean a C_4-C_8 cycloalkyl group fused to a phenyl ring Examples of these groups include benzocyclobutyl, indanyl, 1 2,3 4-tetrahydronaphthyl and the like

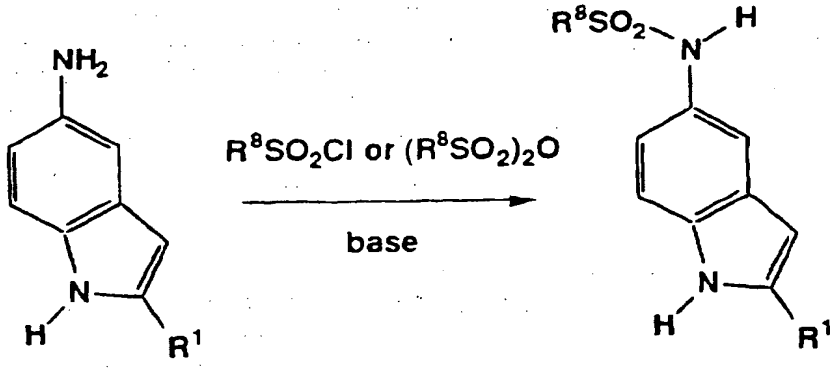
The compounds of Formula IV are prepared by methods well known to one of ordinary skill in the art, such as that generally described in U S #4,443,451, hereby incorporated by reference While the simple indoles required for the preparation of the compounds of this invention are generally commercially available their preparations are described

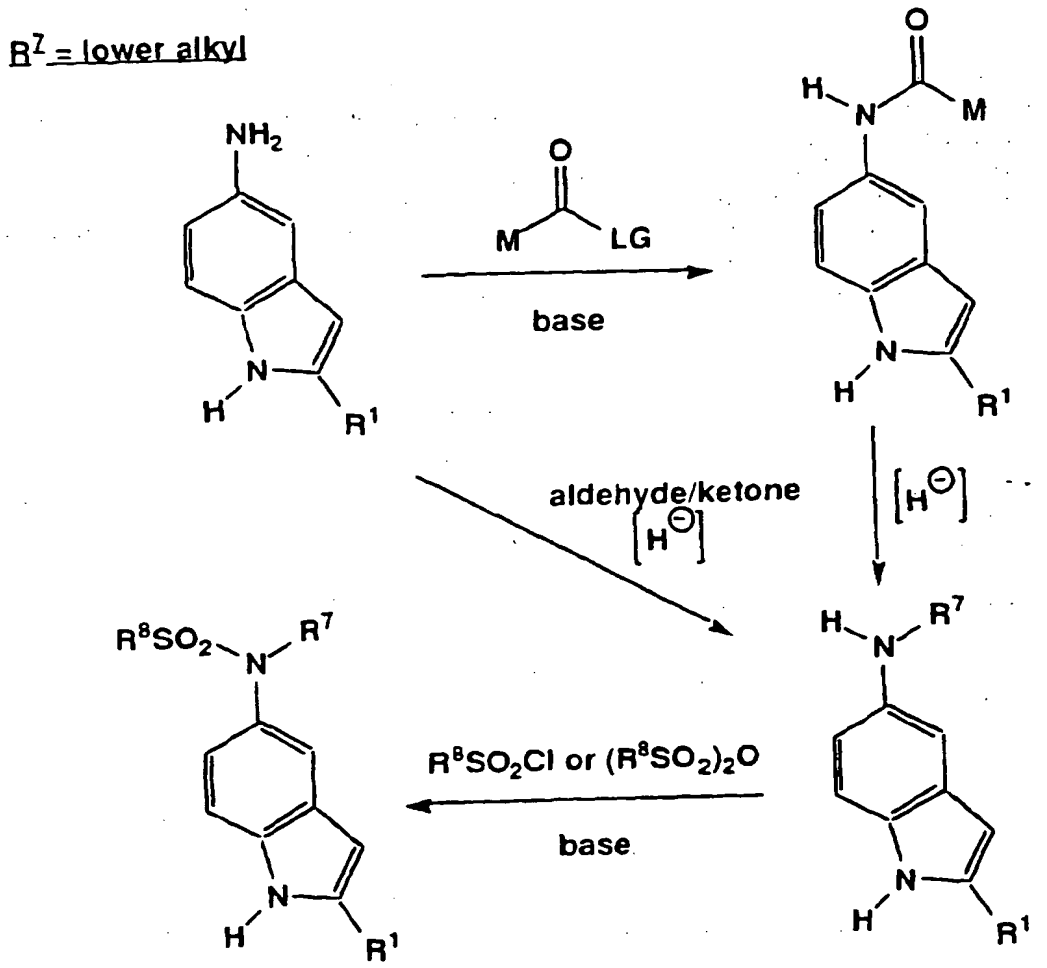
in Robinson. *The Fischer Indole Synthesis*, Wiley New York (1983) Hamel *et al*, *Journal of Organic Chemistry*, 59 6372 (1994) and Russell *et al*. *Organic Preparations and Procedures International*. 17 391 (1985)

The compounds of the invention where X is $-NR^7SO_2R^8$ may be prepared by first modifying an appropriate 5-aminoindole When R^7 is hydrogen the 5-aminoindole is reacted with an appropriate sulfonyl halide or anhydride to give the corresponding sulfonamide When R^7 is lower alkyl however the 5-aminoindole is first acylated and then reduced with an appropriate hydride reducing agent Alternatively the 5-aminoindole may be reductively alkylated with an appropriate aldehyde or ketone in the presence of a suitable hydride reducing agent to give the appropriately substituted indole These substituted indoles are then reacted with a sulfonyl halide or anhydride to give the corresponding sulfonamide This chemistry is illustrated in Synthetic Scheme I, where M is methoxy ethoxy methyl ethyl. propyl or isopropyl, LG is chloro or bromo, and R^1, R^7 and R^8 are as defined *supra*.

Synthetic Scheme I

$R^7 = H$





When R^7 is to be hydrogen, a solution of 5-aminoindole in a suitable solvent such as tetrahydrofuran dioxane. diethyl ether or dimethylformamide. at a temperature from about ambient to about 0°C, is reacted with a commercially available R^8-sulfonyl halide or R^8-sulfonic anhydride in the presence of a suitable base such as pyridine or triethylamine The resultant sulfonamide may be isolated by dilution of the reaction mixture with water, adjustment of pH, and extraction with a water immiscible solvent such as dichloromethane The product may be used for further reaction as recovered or may be purified by chromatography or by recrystallization from a suitable solvent

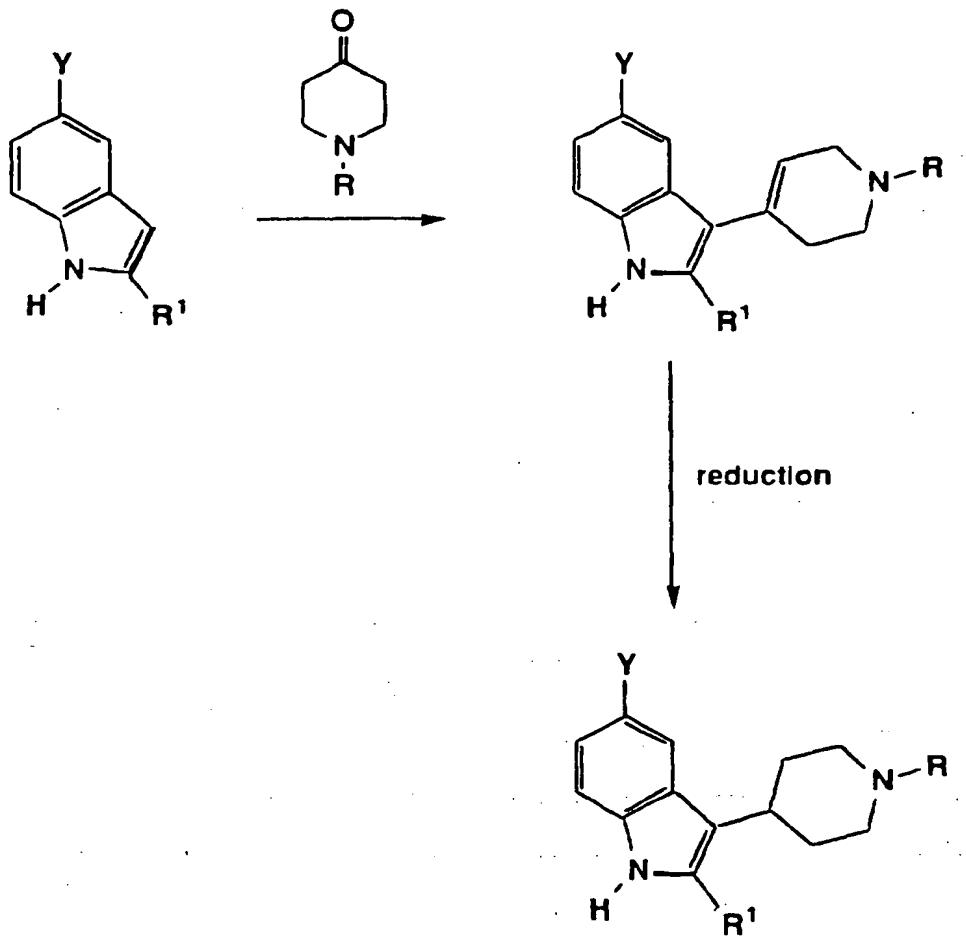
When R^7 is to be lower alkyl, a solution of 5-aminoindole in a suitable solvent, such as tetrahydrofuran dioxane. or diethyl ether. at a temperature from about ambient to about 0°C is reacted with a compound of structure M-C(O)-halo in the presence of a suitable base such as pyridine or triethylamine The resultant compound is isolated by dilution of the reaction mixture with water and extraction with a water immiscible solvent such as dichloromethane This acylated product may either be purified chromatographically or used directly in the subsequent step The acylated product is then dissolved in a suitable solvent. such as tetrahydrofuran or diethyl ether at a temperature from about ambient to about 0°C and is treated with a suitable hydride reducing agent such as diborane or lithium aluminum hydride The reaction is stirred from 1 to 24 hours and is then treated with aqueous solution of sodium sulfate The resultant suspension is filtered, and the filtrate concentrated under reduced pressure The product may be used for further reaction as is purified by chromatography, or recrystallized from a suitable solvent

Alternatively, a solution of a 5-aminoindole in a solvent suitable for the azeotropic removal of water such as toluene. benzene or cyclohexane, is reacted at reflux with an appropriate aldehyde or ketone such as formaldehyde. acetaldehyde propanal, butanal or acetone. in the presence of 0 1-10% of a proton source such as p-toluenesulfonic acid When the reaction is complete the volatiles are removed under reduced pressure and the residue redissolved in an alkanol such as methanol or ethanol This solution is then subjected to hydrogenation conditions, or is treated with an appropriate hydride reducing agent, such as sodium borohydride or preferably sodium cyanoborohydride in the presence of an anhydrous acid such as hydrogen chloride The reaction is then diluted with water tr ated with base and

extracted into a water immiscible solvent such as dichloromethane The product may be used as is for further reaction purified by chromatography or crystallized from a suitable solvent This product is now treated with a commercially available R^8-sulfonyl halide or R^8-sulfonic anhydride as described *supra* to give the required sulfonamides

Compounds of the invention where X is -S-R^2 -C(O)R^3 or-C(O)NR^4R^{15} are prepared by first converting a 5-bromoindole into a 5-bromo-3-(1 2 3 6-tetrahydropyridin-4-yl)-1H-indole or 5-bromo-3-(1-piperidin-4-yl)-1H-indole Compounds of the invention where X is -NR^5R^6 -NHC(O)N$R^{10}R^{11}$, -NHC(O)OR^{12} or-NR^{13}C(O)R^{14} are prepared by first converting a 5-nitro- or 5-aminoindole into a 5-nitro- or 5-amino-3-(1 2 3 6-tetrahydropyridin-4-yl)-1H-indole or into the corresponding 5-nitro- or 5-amino-(1-piperidin-4-yl)-1H-indole Compounds of the invention where X is -N$R^7SO_2R^8$ or -NR^{13}C(O)R^{14} may be prepared by converting the appropriately substituted indole into the corresponding 3-(1 2 3 6-tetrahydropyridin-4-yl)-1H-indole or 3-(1-piperidin-4-yl)-1H-indole This chemistry is illustrated in Synthetic Scheme II where Y is nitro, amino, bromo, -NR^{13}C(O)R^{14} or -N$R^7SO_2R^8$ and R R^1, R^7, R^8, R^{13} and R^{14} are as defined *supra*

Syntheric Scheme II



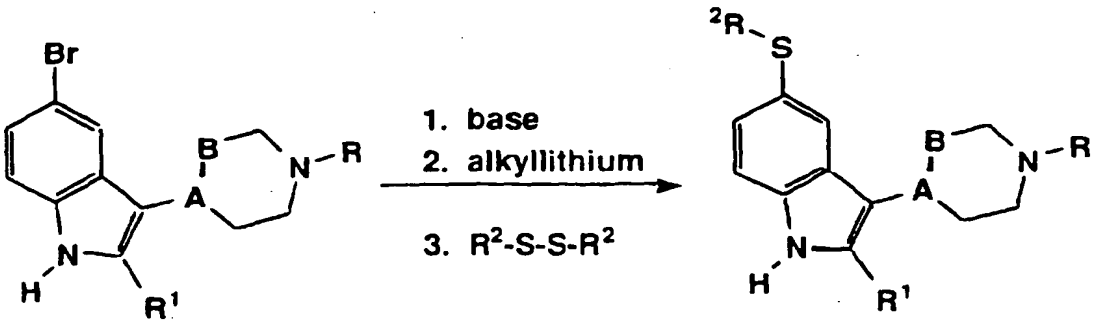
The 5-substituted indole is condensed with a 4-piperidone in the presence of a suitable base to give the corresponding 5-substituted-3-(1.2,3 6-tetrahydropyridin-4-yl)-1H-indole The reaction is performed by first dissolving an excess of the base typically sodium or potassium hydroxide in a lower alkanol. typically methanol or ethanol The indole and two equivalents of the 4-piperidone are then added and the reaction refluxed for 8-72 hours The resulting 5-substituted-3-(1.2 3 6-tetrahydro-pyridin-4-yl)-1H-indoles may be isolated from the reaction mixture by the addition of water Compounds which precipitate may be isolated directly by filtration while others may be extracted by adjusting the pH of the solution and extracting with a water immiscible solvent such as ethyl acetate or dichloromethane The compounds recovered may be used directly in subsequent steps or first purified by silica gel chromatography or recrystallization from a suitable solvent

The 5-substituted-3-(1-substituted-1 2 3 6-tetrahydropyridin-4-yl)-1H-indoles may be used to prepare other compounds of the invention or, if desired may be hydrogenated over a precious metal catalyst such as palladium on carbon to give the corresponding 5-substituted-3-(piperidin-4-yl)-1H-indoles When Y is bromo a hydrogenation catalyst such as sulfided platinum on carbon platinum oxide, or a mixed catalyst system of sulfided platinum on carbon with platinum oxide is used to prevent hydrogenolysis of the 5-bromo substituent during reduction of the tetrahydropyridinyl double bond The hydrogenation solvent may consist of a lower alkanol such as methanol or ethanol tetrahydrofuran or a mixed solvent system of tetrahydrofuran and ethyl acetate The hydrogenation may be performed at an initial hydrogen pressure of 20-80 p s i preferably from 50-60 p s i . at 0-60°C preferably at ambient temperature to 40°C for 1 hour to 3 days Additional charges of hydrogen may be required to drive the reaction to completion depending on the specific substrate The 5-substituted-3-(piperidin-4-yl)-1H-indoles prepared in this manner are isolated by removal of the catalyst by filtration followed by concentration of the reaction solvent under reduced pressure The product recovered may be used directly in a subsequent step or further purified by chromatography or by recrystallization from a suitable solvent

As an alternative to hydrogenation the 5-substituted-3-(1,2 3 6-tetrahydro-4-pyridinyl)-1H-indoles may be converted to the corresponding 5-substituted-3-(piperidin-4-yl)-1H-indoles by treatment with trifluoroacetic acid/triethylsilane if desired The 5-substituted-3-(1-substituted-1 2 5 6-tetrahydro-4-pyridinyl)-1H-indole is dissolved in trifluoroacetic acid to which is added an excess 1 1-10 0 equivalents of triethylsilane The reaction mixture is stirred at about ambient temperature for from about 1 to about 48 hours at which time the reaction mixture is concentrated under reduced pressure The residue is then treated with 2N sodium or potassium hydroxide and the mixture extracted with a water immiscible solvent such as dichloromethane or diethyl ether The resultant 5-substituted-3-(piperidin-4-yl)-1H-indole is purified by column chromatography if desired The skilled artisan will appreciate that the 5-nitro substituent may be reduced before or after condensation with an appropriate 4-piperidone Additionally, the nitro group and the 1.2.3.6-tetrahydropyridinyl double bond may be hydrogenated simultaneously if desired

Compounds where X is -S-R^2 are prepared from the corresponding 5-bromo-3-(1 2 3 6-tetrahydropyridin-4-yl)-1H-indoles or 5-bromo-3-(piperidin-4-yl)-1H-indoles as illustrated in Synthetic Scheme III, where A, B, R^1 and R^2 are as defined *supra* and R = C_1-C_4 alkyl

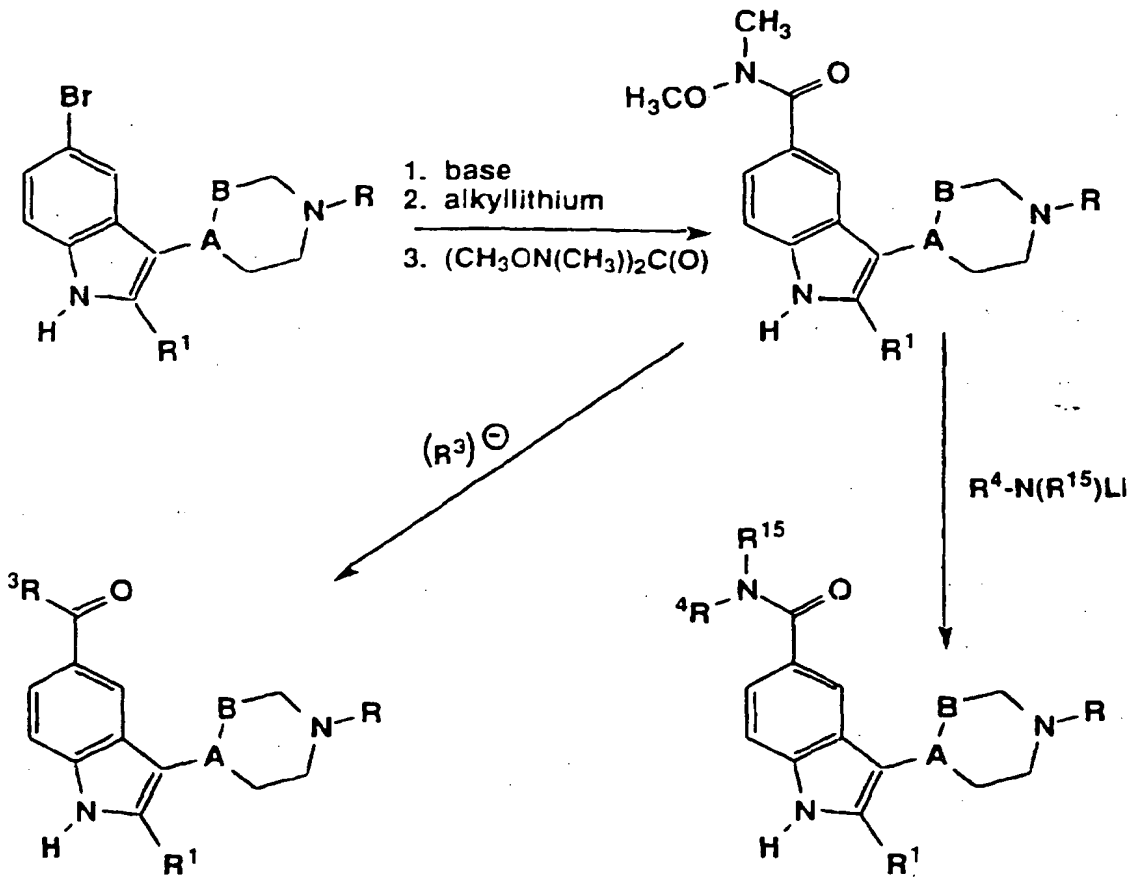
Synthetic Scheme III



The 5-bromo-3-(1 2,3,6-tetrahydropyridin-4-yl)-1H-indoles or 5-bromo-3-(piperidin-4-yl)-1H-indoles in a suitable aprotic solvent, such as diethyl ether or tetrahydrofuran are cooled to about 0°C and treated with potassium hydride to deprotonate the indole nucleus at the 1-position While other hydrides are useful for this deprotonation the resultant potassium salt is more soluble in typical reaction solvents The reaction mixture is then cooled to about -78°C and halogen-metal exchange effected by the addition of two equivalents of t-butyllithium To this dianion solution are then added an appropriate disulfide and the reaction mixture allowed to warm to ambient temperature The compound of the invention is isolated by treating the reaction mixture with aqueous base, such as sodium or potassium hydroxide, and then extracting with a water immisible solvent such as diethyl ether or dichloromethane The reaction product may then be purified by column chromatography

Compounds where X is -C(O)R^3 or -C(O)NR^4R^{15} are prepared from the corresponding 5-bromo-3-(1,2 3.6-tetrahydropyridin-4-yl)-1H-indoles or 5-bromo-3-(piperidin-4-yl)-1H-indoles as illustrated in Synthetic Scheme IV, where A, B R^1, R^3 R^4 and R^{15} are as defined *supra* and R = C_1-C_4 alkyl

Synthetic Scheme IV



The dianion of the 5-bromo-3-(1 2 3 6-tetrahydropyridin-4-yl)-1H-indoles or 5-bromo-3-(1-substituted-piperidin-4-yl)-1H-indole prepared as described *supra*, is then treated with N N'-dimethyl-N,N'-dimethoxyurea The resulting N-methyl-N-methoxy-5-carboxamido-1H-indole is isolated by treating the reaction mixture with aqueous base, such as sodium or potassium hydroxide and then extracting with a water immisible solvent such as diethyl ether or dichloromethane The reaction product may then be purified by column chromatography

Compounds where X is -C(O)R^3 are prepared by reacting a solution of the N-methyl-N-methoxy-5-carboxamido-3-(1 2 3 6-tetrahydropyridin-4-yl)-1H-indole or N-methyl-N-methoxy-5-carboxamido-3-(piperidin-4-yl)-1H-indole in a suitable solvent such as diethyl ether or tetrahydrofuran at about 0°C with an appropriate reagent such as an aryl- or alkyllithium or an alkyl or aryl Grignard reagent These reagents are either commercially available or may be prepared by methods well known to one of ordinary skill in the art The aryl- or alkyllithium reagents are conveniently prepared by treating an appropriate aryl or alkyl halide with n-butyllithium The aryl or alkyl Grignard reagents may be prepared by treating an appropriate aryl or alkyl halide with magnesium The compounds of interest may be isolated by aqueous work-up followed by extraction into a water immiscible solvent such as diethyl ether or dichloromethane, and then purified by chromatography or by recrystallization from a suitable solvent

The skilled artisan will also appreciate that the compounds where X is -C(O)R^3 are also available by the reaction of the dianion of either a 5-bromo-3-(1,2 3 6-tetrahydropyridin-4-yl)-1H-indole or a 5-bromo-3-(piperidin-4-yl)-1H-indole with an appropriate aryl or alkyl N-methyl-N-methoxycarboxamide These carboxamides are prepared from the corresponding carboxylic acids and N-methyl-N-methoxyamine under standard peptide coupling conditions using N N'-dicyclohexylcarbodiimide

Compounds where X is -C(O)NR^4R^{15} are prepared by reacting a solution of the N-methyl-N-methoxy-5-carboxamido-3-(1,2 3,6-tetrahydropyridin-4-yl)-1H-indole or N-methyl-N-methoxy-5-carboxamido-3-(piperidin-4-yl)-1H-indole in a suitable solvent such as diethyl ether or tetrahydrofuran at about 0°C with the anion of an appropriate amine

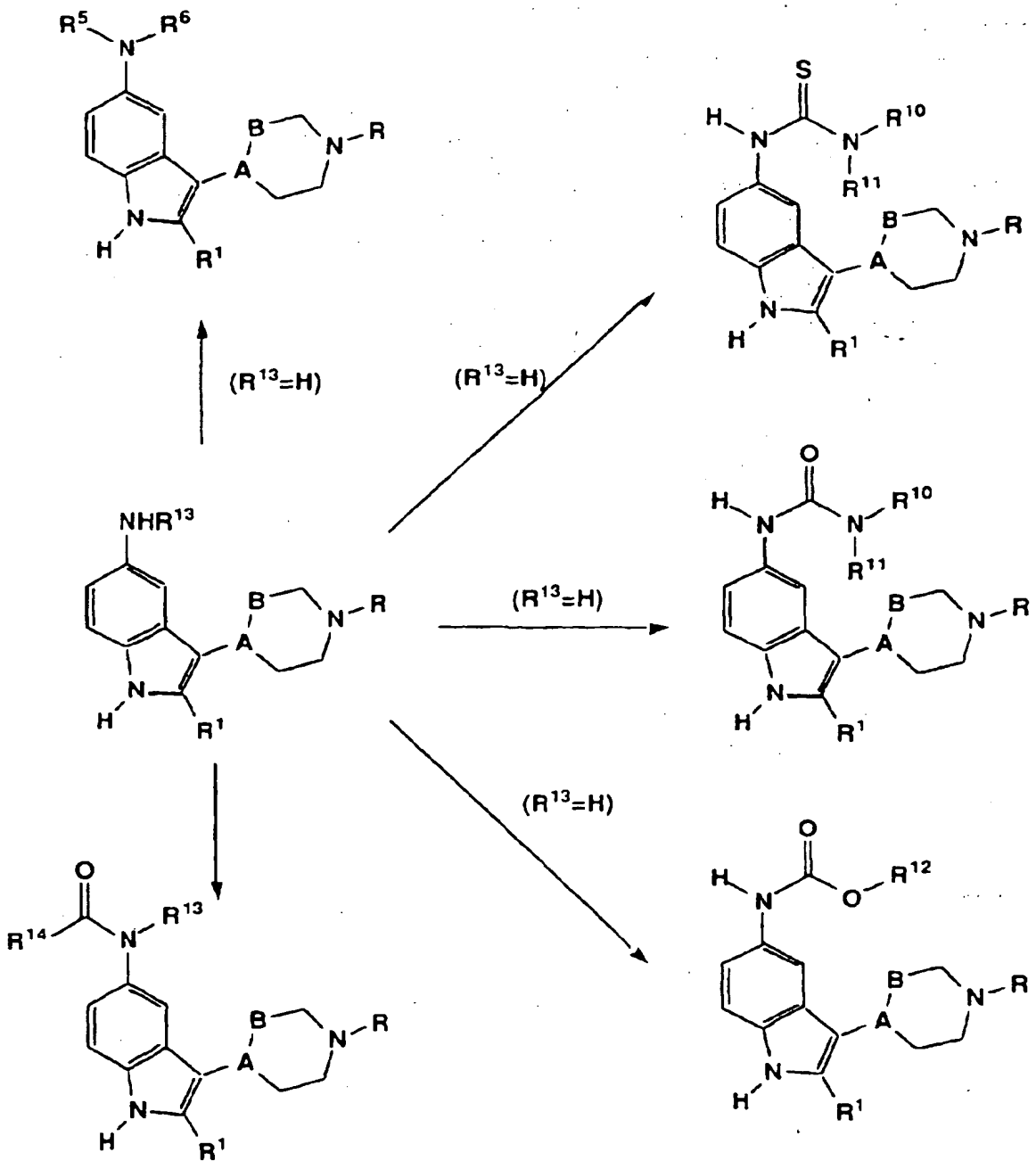
These anions are prepared by treating the appropriate amine with n-butyllithium The compounds of interest may be isolated by aqueous work-up followed by extraction into a water immiscible solvent such as diethyl ether or dichloromethane and then purified by chromatography. or by recrystallization from a suitabl solvent

Alternatively compounds where X is -C(O)NR^{4}R^{15} are prepared by subjecting an appropriate indole 5-carboxylic acid and an appropriate amine to standard peptide coupling conditions The indole 5-carboxylic acid in an appropriate solvent may be treated with oxalyl chloride. thionyl chloride or phosphorous tribromide in an appropriate solvent. for example toluene. to prepare the corresponding acid halide The acid halide in a suitable solvent, for example tetrahydrofuran or dimethylformamide may be treated with an amine of formula HNR^{4}R^{14} in the presence of a suitable base such as triethylamine pyridine or dimethylaminopyridine to provide the desired compound The product may be isolated by aqueous work-up followed by extraction into a water immiscible solvent such as diethyl ether ethyl acetate or dichloromethane and then purified by chromatography, or by recrystallization from a suitable solvent

Preferably compounds where X is -C(O)NR^{4}R^{15} are prepared by reacting the appropriate indole 5-carboxylic acid with an appropriate amine in the presence of typical peptide coupling reagents such as N N'-carbonyldiimidazole (CDI). N,N'-dicyclohexylcarbodiimide (DCC) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC)

Compounds where X is -NR^{5}R^6 -NHC(Q)NR^{10}R^{11} -NHC(O)OR^{12} or -NR^{13}C(O)R^{14} are prepared by reacting the appropriate 5-amino-3-(1,2 3,6-tetrahydropyridin-4-yl)-1H-indole or 5-amino-3-(piperidin-4-yl)-1H-indole with a suitable electrophile These reactions are illustrated in Synthetic Scheme V where A, B, R^1, R^5 R^6, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are as described *supra* and R = C_1-C_4 alkyl

Synthetic Scheme V



Compounds where X is -NR^5R^6 are prepared by treating a solution of the 5-amino-3-(1 2,3 6-tetrahydropyridin-4-yl)-1H-indole or 5-amino-3-(piperidin-4-yl)-1H-indole in a suitable solvent. such as dichloromethane, tetrahydrofuran, acetonitrile or dimethylformamide, with a suitable electrophile such as trifluoromethanesulfonic anhydride or N-carbethoxyphthalimide, in the presence of a suitable base such as pyridine or triethylamine The reaction product is isolated by evaporation of the reaction solvent under reduced pressure The product may be purified by chromatography or by crystallization from an appropriate solvent

Compounds where X is -$NBC(Q)NR^{10}R^{11}$ are prepared by treating a solution of the 5-amino-3-(1.2 3 6-tetrahy-

dropyridin-4-yl)-1H-indole or 5-amino-3-(piperidin-4-yl)-1H-indole in a suitable solvent such as chloroform or dichloromethane with an appropriate isocyanate isothiocyanate carbamoyl chloride or carbamoyl bromide Appropriate carbamoyl chlorides are available by treating an amine of formula $HNR^{10}R^{11}$ with phosgene When a carbamoyl chloride or carbamoyl bromide is used the reactions are performed in the presence of a suitable base Suitable bases include amines typically used as acid scavengers such as pyridine or triethylamine. or commercially available polymer bound bases such as polyvinylpyridine If necessary an excess of the isocyanate. isothiocyanate carbamoyl chloride or carbamoyl bromide is employed to ensure complete reaction of the starting amine The reactions are performed at about ambient to about 80°C for from about three hours to about three days Typically the product may be isolated by washing the reaction mixture with water and concentrating the remaining organics under reduced pressure When an excess of isocyanate isothiocyanate carbamoyl chloride or carbamoyl bromide has been used however a polymer bound primary or secondary amine. such as an aminomethylated polystyrene, may be conveniently added to react with the excess reagent Isolation of products from reactions where a polymer bound reagent has been used is greatly simplified. requiring only filtration of the reaction mixture and then concentration of the filtrate under reduced pressure The product from these reactions may be purified chromatographically or recrystallized from a suitable solvent if desired The skilled artisan will appreciate that compounds which are ureas may be converted into the corresponding thiourea by treatment with [2,4-bis(4-methoxyphenyl)-1 3-dithia-2.4-diphosphetane-2 4-disulfide] (Lawesson's Reagent) or phosphorus pentasulfide

Compounds where X is $-NHC(O)OR^{12}$ are prepared by reacting the 5-amino-3-(1 2 3,6-tetrahydropyridin-4-yl)-1H-indole or 5-amino-3-(piperidin-4-yl)-1H-indole with an appropriately substituted chloroformate in the presence of a suitable amine under the conditions described in the previous paragraph Likewise, compounds where X is $-NR^{13}C(O)R^{14}$ are prepared by reacting the 5-amino-3-(1,2 3 6-tetrahydropyridin-4-yl)-1H-indole or 5-amino-3-(piperidin-4-yl)-1H-indole with an appropriate carboxylic acid chloride bromide or anhydride, optionally in the presence of an acylation catalyst such as dimethylaminopyridine, in the presence of a suitable base, such as those described *supra*

Alternatively, compounds where X is $-NR^{13}C(O)R^{14}$ are prepared by reacting the 5-amino-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole or 5-amino-3-(piperidin-4-yl)-1H-indole with an appropriate carboxylic acid halide carboxylic acid anhydride, or a carboxylic acid in the presence of typical peptide coupling reagents such as N,N'-carbonyldiimidazole (CDI), N,N'-dicyclohexylcarbodiimide (DCC) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) A polymer supported form of EDC has been described (*Tetrahedron Letters*, **34**(48), 7685 (1993)) and is very useful for the preparation of the compounds of the present invention The product from these reactions is isolated and purified as described above

The skilled artisan will appreciate that the order in which the steps are performed to prepare these compounds is not important in many cases For example, compounds where X is $-NR^{7}SO_2R^{8}$ are accessible by subjecting the 5-amino-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indoles or 5-amino-3-(piperidin-4-yl)-1H-indoles to the conditions illustrated in Synthetic Scheme I Likewise, 5-aminoindole may be subjected to the reaction sequences illustrated in Synthetic Scheme V prior to reaction with a 4-piperidone as illustrated in Synthetic Scheme II The skilled artisan will also appreciate that compounds where R is H may be prepared by condensing 4-piperidone with a suitably substituted indole to give the corresponding 3-(1.2.3.6-tetrahydropyridin-4-yl)-1H-indoles which may then be hydrogenated if desired Alternatively 1-benzyl-4-piperidone may be substituted at any point in the synthesis for a suitably substituted 4-piperidone The benzyl group may then be removed by standard hydrogenation conditions after reactions for which the secondary amine would be incompatible are complete The 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indoles may also be reduced to the corresponding 3-(piperidin-4-yl)-1H-indoles at any convenient point in the synthetic sequence These variations are made apparent in the following Preparations and Examples

PREPARATION I

5-bromo-3-(1-methylpiperidin-4-yl)-1H-indole

Preparation of 5-bromo-3-(1-methyl-1.2 3,6-tetrahydropyridin-4-yl)-1H-indole

To a solution of 56 11 gm (306 mMol) potassium hydroxide in 300 mL methanol were added 38 mL (306 mMol) 1-methyl-4-piperidone followed by 30 0 gm (153 mMol) 5-bromo-1H-indole The reaction mixture was stirred at reflux for 18 hours The reaction mixture was then cooled to ambient and diluted with 1 5 L water The resultant white solid was filtered. washed sequentially with water and diethyl ether and then dried under vacuum to give 44 6 gm (100%) 5-bromo-3-(1-methyl-1 2,3 6-tetrahydro-4-pyridinyl)-1H-indole

Catalytic hydrogenation

To a solution of 44 6 gm (153 mMol) 5-bromo-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole in 1 95 L tet-

rahydrofuran were added 9 0 gm platinum oxide The reaction mixture was hydrogenated with an initial hydrogen pressure of 60 p s i at ambient temperature for 24 hours The reaction mixture was filtered and the filtrate concentrated under reduced pressure The residue was recrystallized from acetonitrile to give 32 6 gm (73 7%) of the title compound as a white solid

MS(m/e) 293(M^+)

Calculated for $C_{14}H_{17}N_2Br$ Theory C 57 32 H 5 96 N 9 69 Found C 57 35 H 5 84 N 9 55

PREPARATION II

N-methyl-N-methoxy-5-carboxamido-3-(1-methylpiperidin-4-yl)-1H-indole

To a suspension of 0 72 gm (3 58 mMol) potassium hydride in 16 0 mL tetrahydrofuran at 0°C was added a solution of 1 0 gm (3 41 mMol) 5-bromo-3-(1-methylpiperidin-4-yl)-1H-indole in 16 0 mL tetrahydrofuran and the solution stirred for about 30 minutes The resulting mixture was cooled to about -78°C and to it were added 4 4 mL (7 5 mMol) t-butyl lithium, which had been precooled to -78°C via cannula After about 15 minutes 0 66 gm (3 41 mMol) N N'-dimethyl-N,N'-dimethoxyurea were added and the reaction mixture was allowed to warm gradually to ambient The reaction mixture was then treated with 5N sodium hydroxide and extracted with diethyl ether The ether extracts were combined washed with saturated aqueous sodium chloride dried over sodium sulfate and concentrated under reduced pressure Purification by flash chromatography eluting with 4 5 0 5 0 2 ethyl acetate methanol toluene gave 0 81 gm (60%) of the title compound

MS(m/e) 301(M^+)

IR 1632 cm^{-1}

Calculated for $C_{17}H_{23}N_3O_2 \cdot 0\ 25\ H_2O$ Theory C 66 75 H 7 74 N, 13 73 Found C 66 47 H 7 72 N 13 69

PREPARATION III

2-methyl-5-amino-1H-indole

To a solution of 2 0 gm (11 4 mMol) 2-methyl-5-nitro-1H-indole in 100 mL 1 1 ethanol tetrahydrofuran were added 0 25 gm 5% palladium on carbon The suspension was hydrogenated at ambient temperature at an initial hydrogen pressure of 60 p s i After 5 hours the reaction mixture was filtered and the filtrate concentrated under reduced pressure to give 1 5 gm of a dark brown solid The solid was purified by flash chromatography, eluting with a gradient of dichloromethane containing 0-3% methanol to give 1 19 gm (71 7%) of the title compound as light brown plates

m p =154-156°C

MS(m/e) 147(M+1)

Calculated for $C_9H_{10}N_2$ Theory C 73 94, H, 6 89 N 19 16 Found C 74 15 H 6 93 N 19 27

Many of the 5-(C_1-C_4 alkyl)amino-1H-indoles required for the preparation of compounds of the invention are available through the procedure described in Preparation IV

PREPARATION IV

5-methylamino-1H-indole

A Preparation of N-ethoxycarbonyl-5-amino-1H-indole

To a solution of 4 27 gm (32 3 mMol) 5-amino-1H-indole in 50 mL tetrahydrofuran were added 5 4 mL (38 8 mMol) triethylamine and the reaction mixture was then cooled to 0°C To this solution were then added dropwise 3 4 mL (35 5 mMol) ethyl chloroformate After 4 hours the reaction mixture was diluted with 1N HCl and was then extracted with ethyl acetate The organic phase was washed sequentially with 1N HCl water and saturated aqueous sodium chloride The remaining organics were dried over sodium sulfate and concentrated under reduced pressure to give 7 4 gm of a dark oil This oil was purified by flash chromatography eluting with a gradient of dichloromethane containing 0-2 5% methanol, to give 4 95 gm (75%) of the title compound as a tan solid

m p =113-114°C

MS(m/e) 204(M^+)

Calculated for $C_{11}H_{12}N_2O_2$ Theory C 64 69 H 5 92 N 13 72 Found C 64 76 H 5 92 N 13 76

B Reduction of N-ethoxycarbonyl-5-amino-1H-indole

To a suspension of 6 3 gm (164 5 mMol) lithium aluminum hydride in 50 mL tetrahydrofuran was added dropwise a solution of 4 8 gm (23 5 mMol) N-ethoxycarbonyl-5-amino-1H-indole in 40 mL tetrahydrofuran The reaction mixture was heated to reflux until the starting material was consumed as measured by thin-layer chromatography The reaction mixture was then cooled to ambient and treated with saturated aqueous sodium sulfate to destroy excess lithium aluminum hydride The resulting suspension was filtered and the filtrate concentrated under reduced pressure to give 3 6 gm of a dark solid The solid was subjected to flash chromatography, eluting with a gradient of dichloromethane containing 0-2% methanol to give 3 3 gm (97 1%) of the title compound as a tan solid
MS(m/e) 146(M^+)
Calculated for $C_9H_{10}N_2$ Theory C 73.94, H, 6 90, N 19 16 Found C, 73 78, H, 6 94 N, 19 04

All of the 5-sulfonamido-1H-indoles required for the preparation of compounds of the invention are available by treating 5-amino-1H-indole with an appropriate sulfonyl chloride as described in Preparation V

PREPARATION V

5-methanesulfonamido-1H-indole

To a solution of 2 0 gm (15 1 mMol) 5-amino-1H-indole in 25 mL tetrahydrofuran were added 2 4 mL (17 2 mMol) triethylamine The reaction mixture was cooled in an ice bath as 1 23 mL (15 9 mMol) methanesulfonyl chloride were added dropwise. After 3 5 hours the reaction mixture was partitioned between 1N sodium hydroxide and ethyl acetate The organic phase was extracted twice with 1N sodium hydroxide All sodium hydroxide phases were combined, adjusted to pH=5 with acid and extracted well with ethyl acetate These organic phases were combined washed sequentially with water and saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure to give 3 0 gm of a purple solid This solid was crystallized from cyclohexane/ethyl acetate to give 2.5 gm (78 6%) of the title compound as light purple crystals m p =133-135°C
MS(m/e) 210(M^+)
Calculated for $C_9H_{13}N_2O_2S$ Theory C, 51 41; H, 4 79, N, 13 32 Found C 51 16, H, 4 93, N, 13 27

PREPARATION VI

5-amino-3-(1-methylpiperidin-4-yl)-1H-indole

A From 5-nitro-1H-indole

To a solution of 10 38 gm (185 mMol) potassium hydroxide in 200 mL methanol were added 10 0 gm (61 7 mMol) 5-nitro-1H-indole followed by 13 96 gm (123 mMol) 1-methyl-4-piperidone The mixture was heated to reflux for 4 days under a nitrogen atmosphere The reaction mixture was then allowed to cool to ambient and the solid which formed filtered and washed with methanol This solid was dried under vacuum at 50°C The combined filtrates were then concentrated under reduced pressure and the residue subjected to flash chromatography, eluting with 92 5 7 5 dichloromethane methanol Fractions shown to contain product were combined and concentrated under reduced pressure This solid was combined with that isolated directly from the reaction mixture to give 13 79 gm (87%) 5-nitro-3-(1-methyl-1 2,3,6-tetrahydropyridin-4-yl)-1H-indole

To a solution of 38 2 gm (145 mMol) 5-nitro-3-(1-methyl-1 2,3 6-tetrahydropyridin-4-yl)-1H-indole in 1 9 L ethanol and 30 mL 5N HCl were added 10 0 gm 5% palladium on carbon The reaction mixture was hydrogenated at ambient for 18 hours with an initial hydrogen pressure of 60 p s i The reaction mixture was filtered and then concentrated under reduced pressure The residue was dissolved in methanol and the solution filtered This filtrate was concentrated under reduced pressure and the residue redissolved in ethanol The solution was concentrated to about 500 mL and product allowed to crystallize The crystals were filtered to give 48 9 gm (95%) of the title compound as its dihydrochloride salt, ethanol solvate
m p =310-320°C (dec)
MS(m/e) 229(M^+)
Calculated for $C_{14}H_{19}N_3 \cdot 2HCl \cdot C_2H_6O$ Theory C 55 17, H, 7 81 N 12 06 Found C 55 23, H 7 61 N 12 30

B Via 5-amino-1H-indole

To a solution of 1 29 gm (20 mMol) potassium hydroxide in 10 mL methanol were added 1 32 gm (10 mMol) 5-amino-1H-indole followed by 2 46 mL (20 mMol) 1-methyl-4-piperidone The reaction mixture was then heated to

reflux for 18 hours The reaction mixture was ccoled to ambient diluted with 20 ml water and the precipitate collected by filtration The solid was recrystallized from ethyl acetate methancl to give 1 11 gm (48 9%) 5-amino-3-methyl-1.2 3 6-tetrahydropyr-idin-4-yl)-1H-indole as a tan solid (m p =200-203°C) The tan solid was subjected to flash chromatography eluting with 100 20 0 5 dichloromethane methanol ammonium hydroxide. to give 0 99 gm 5-amino-3-(1-methyl-1 2 3 6-tetrahydropyridin-4-yl)-1H-indole as a cream colored solid (m p =212-215°C (ethyl acetate methanol))

MS(m/e) 227(M^+)

Calculated for $C_{14}H_{17}N_3$ Theory C 73 98 H 7 54 N 18 49 Found C 73 76 H 7 48 N 18 22

To a solution of 11 3 gm (50 mMol) 5-amino-3-(1-methyl-1 2 3 6-tetrahydropyridin-4-yl)-1H-indole in 250 mL methanol were added 3 0 gm 5% palladium on carbon The mixture was hydrogenated at room temperature under an initial hydrogen pressure of 60 p s i for 18 hours The reaction mixture was filtered and the filtrate concentrated under reduced pressure to give a dark gum which was slurried in hexane to give the title compound as a brown solid

MS(m/e) 229(M^+)

PREPARATION VII

4-chloro-N-methyl-N-methoxybenzamide

To a solution of 11 38 gm (116 7 mMol) N-methoxy-N-methyl amine hydrochloride in 700 mL 1N sodium hydroxide was added a solution of 18 56 gm (106 04 mMol) 4-chlorobenzoyl chloride in 200 mL dichloromethane and the mixture was stirred at ambient After 18 hours the phases were separated and the remaining aqueous was extracted well with dichloromethane All organic phases were combined dried over sodium sulfate and concentrated under reduced pressure to give 27 9 gm (95%) of the title compound as a clear oil

MS(m/e) 165(M^-)

IR 3011 2974 2938 1634 cm^{-1}

PREPARATION VIII

5-carboxy-3-(1-methyl-1 2 5,6-tetrahydropyridin-4-yl)-1H-indole

To a solution of 5 8 gm (90 mMol) potassium hydroxide in 50 mL methanol were added 4 83 gm (30 mMol) indole 5-carboxylic acid followed by 7 4 mL (60 mMol) 1-methyl-4-piperidone and the resulting solution was heated at reflux for 18 hours The reaction mixture was then concentrated under reduced pressure and the resulting oil dissolved in 200 mL water The solution was gradually neutralized by addition of 18 mL 5 N hydrochloric acid The precipitate which formed was isolated by filtration and washed with water to provide 6 09 gm after drying This solid was dissolved in 100 mL 0 5 N sodium hydroxide, filtered and the filtrate treated with 50 mL 1N hydrochloric acid The solid which formed was filtered and dried under reduced pressure to provide 5 46 gm (71%) of the title compound

m p =249°C

MS(m/e) 256(M^+)

Calculated for $C_{15}H_{16}N_2O_2$ Theory C 70 29 H 6 29 N 10 93 Found C 70 02 H, 6 39 N 11 02

PREPARATION IX

5-carboxy-3-(1-methylpiperidin-4-yl)-1H-indole

5-ethoxycarbonyl-3-(1-methyl-1 2 5 6-tetrahydropyridin-4-yl)-1H-indole

A solution of 0 513 gm (2 mMol) 5-carboxy-3-(1-methyl-1.2 5 6-tetrahydropyridin-4-yl)-1H-indole in 5 1 mL ethanol was cooled in an ice bath while 0 51 mL sulfuric acid was added dropwise The resulting mixture was heated at reflux for 5 hours The now homogeneous solution was poured into 50 mL cold water and was then made basic with saturated ammonium hydroxide The light yellow precipitate was collected by filtration and then recrystallized from ethanol to provide 0 24 gm (42%) of the desired compound as light yellow crystals

m p =249°C

MS(m/e) 284 (M^+)

Calculated for $C_{17}H_{20}N_2O_2$ Theory C. 71 81 H, 7 09 N 9 85 Found C 71 97 H 7 25 N, 9 71

5-ethoxycarbonyl-3-(1-methylpiperidin-4-yl)-1H-indole

To a solution of 3 24 gm (11 3 mMol) 5-ethoxycarbonyl-3-(1-methyl-1 2 5.6-tetrahydropyridin-4-yl)-1H-indole in 100 mL ethanol was added 0 8 gm 5% palladium an carbon and the reaction mixture hydrogenated at room temperature for 18 hours at an initial hydrogen pressure of 60 p s i The reaction mixture was filtered and the filtrate concentrated under reduced pressure The residual oil which crystallized on standing at room temperature was recrystallized from 30 mL acetonitrile to provide 1 79 gm (55%) of the desired compound as colorless crystals
m p =155-157°C
MS(m/e) 286(M^+)
Calculated for $C_{17}H_{22}N_2O_2$ Theory C 71 30. H 7 74 N 9 78 Found C 71 07 H 7 88 N 9 73

Saponification/protonation

A mixture of 0 859 gm (3 mMol) 5-ethoxycarbonyl-3-(1-methylpiperidin-4-yl)-1H-indole, 6 0 mL ethanol and 6 mL 2N sodium hydroxide were heated at reflux for 2 hours Ethanol was distilled from the resulting solution and the remaining aqueous solution was neutralized with 2 4 mL 5N hydrochloric acid The resulting oil suspended in water is treated with a small amount of dichloromethane and cooled The resulting solid is filtered washed with water and acetone and then recrystallized from 15 mL water to provide 0 308 gm (40%) of the title compound as colorless crystals
m p >280°C
MS(m/e) 258(M^+)
Calculated for $C_{15}H_{18}N_2O_2$ Theory C, 69 74. H, 7 02 N, 10 84 Found C. 69 66, H, 7 03 N, 10 92

PREPARATION X

Preparation of a polystyrene bound isocyanate resin

To a stirred suspension of 50 gm (61 mMol) aminomethylated polystyrene resin (1 22 mMol/gm) in 800 mL toluene was added 193 mL (366 mMol) 1 9 M phosgene in toluene After stirring the reaction mixture for 10 minutes. 67 mL (482 mMol) triethylamine was added and the reaction mixture was stirred for 18 hours at room temperature The mixture was filtered and the recovered solid washed with 10 times with dichloromethane A light pink resin mixed with a white solid was obtained This solid mixture was resuspended in 700 mL dichloromethane, stirred for 10 minutes and then filtered and washed well with dichloromethane The resulting solid was again suspended stirred and washed with dichloromethane to provide the desired resin
IR(KBr) 2252 cm^{-1} (characteristic peak for -N=C=O)

EXAMPLE 1

5-phenylthio-3-(1-methylpiperidin-4-yl)-1H-indole

To a suspension of 0 21 gm (1 05 mMol) potassium hydride in 5 0 mL tetrahydrofuran at 0°C was added a solution of 0 3 gm (1 0 mMol) 5-bromo-3-(1-methylpiperidin-4-yl)-1H-indole in 5 0 mL tetrahydrofuran and the solution stirred for about 30 minutes The resulting mixture was cooled to about -78°C and to it were added 1 47 mL (2 3 mMol) t-butyllithium. which had been precooled to -78°C via cannula After about 15 minutes, 0 43 gm (2 mMol) diphenyl disulfide were added and the reaction mixture was allowed to warm gradually to ambient. The reaction mixture was then treated with 5N sodium hydroxide and extracted with diethyl ether The ether extracts were combined. washed with saturated aqueous sodium chloride dried over sodium sulfate and concentrated under reduced pressure Purification by flash chromatography eluting with 4 5 0 5 0 2 ethyl acetate methanol toluene, followed by recrystallization from hexane diethyl ether gave 0 28 gm (85 1%) of the title compound as a white solid
m p =147-150°C
MS(m/e) 322(M^+)
Calculated for $C_{20}H_{22}N_2S$ Theory C 74 49. H 6 89 N. 8 69 Found C 74 27. H, 6 96 N, 8 77
The compounds of Examples 2-5 were prepared employing the method described in detail in Example 1

EXAMPLE 2

5-(4-methoxyphenyl)thio-3-(1-methylpiperidin-4-yl)-1H-indole

Using 0 3 gm (1 0 mMol) 5-bromo-3-(1-methylpiperidin-4-yl)-1H-indole and 0 55 gm (1 99 mMol) di(4-methoxy-

phenyl) disulfide gave 0 28 gm (64 0%) of the title compound as a colorless solid
m p =160-162°C
MS(m/e) 352(M^-)
Calculated for $C_{21}H_{24}N_2OS$ Theory C 71 55 H 6 86 N 7 95 Found C 71 57 H 6 89 N 8 24

EXAMPLE 3

5-benzylthio-3-(1-methylpiperidin-4-yl)-1H-indole

Using 0 325 gm (1 11 mMol) 5-bromo-3-(1-methylpiperidin-4-yl)-1H-indole and 0 55 gm (2 22 mMol) dibenzyl disulfide gave 0 065 gm (17 0%) of the title compound as a colorless solid
m p =138-141°C
MS (m/e) 336(M^+)
Calculated for $C_{21}H_{24}N_2S$ Theory C 74 96, H 7 19, N, 8 33 Found C 75 55 H 7 32, N 7 95

EXAMPLE 4

5-(pyridin-2-yl)thio-3-(1-methylpiperidin-4-yl)-1H-indole

Using 0 3 gm (1 0 mMol) 5-bromo-3-(1-methylpiperidin-4-yl)-1H-indole and 0 44 gm (1 99 mMol) di(pyridin-2-yl) disulfide gave 0 12 gm (37 0%) of the title compound as an off-white solid m p =83°C
MS(m/e) 323(M^+)
Calculated for $C_{19}H_{21}N_3S$ Theory C 70 55 H 6 54 N 12 99 Found C 70 25 H 6 60, N 12 80

EXAMPLE 5

5-(4-chlorophenyl)thio-3-(1-methylpiperidin-4-yl)-1H-indole

Using 0 4 gm (1 36 mMol) 5-bromo-3-(1-methylpiperidin-4-yl)-1H-indole and 0 78 gm (2 73 mMol) di(4-chlorophenyl) disulfide gave 0 39 gm (79 6%) of the title compound as a colorless solid
m p =148-150°C
MS(m/e) 356(M^+)
Calculated for $C_{20}H_{21}N_2SCl$ Theory C 67 30 H 5 93 N 7 85 Found C 67 47 H 6 10 N 7 84

EXAMPLE 6

5-benzoyl-3-(1-methylpiperidin-4-yl)-1H-indole

To a solution of 0 41 mL (0 73 mMol) phenyllithium in 4 0 mL tetrahydrofuran at 0°C were added 0 10 gm (0 33 mMol) N-methyl-N-methoxy-5-carboxamido-3-(1-methylpiperidin-4-yl)-1H-indole (Preparation II) in 2 0 mL tetrahydrofuran After 1 hour the reaction mixture was quenched with 2N sodium hydroxide and the mixture extracted well with diethyl ether The ether extracts were then washed with saturated aqueous sodium chloride dried over sodium sulfate and concentrated under reduced pressure The residue was purified by radial chromatography (2 mm silica) eluting with 10 1 dichloromethane methanol, to give 0 096 gm (91%) of the title compound as a light yellow solid
m p =101°C
MS(m/e) 319(M^+)
IR 1644 cm^{-1}
Calculated for $C_{21}H_{22}N_2O \cdot H_2O$ Theory C, 74 48 H 7 19 N 8 33 Found C, 74 85 H 7 00 N, 8 67

The compounds of Examples 7-9 were prepared employing the method described in detail in Example 6

EXAMPLE 7

5-acetyl-3-(1-methylpiperidin-4-yl)-1H-indole hydrochloride monohydrate

Using 0 30 gm (1 0 mMol) N-methyl-N-methoxy-5-carboxamido-3-(1-methylpiperidin-4-yl)-1H-indole (Preparation II) and 3 56 mL (4 98 mMol) methyllithium gave 5-acetyl-3-(1-methylpiperidin-4-yl)-1H-indole which was converted to its hydrochloride salt 0 153 gm (60%) of the title compound were recovered
m p =65°C

MS(m/e) 256(M^+)
Calculated for $C_{16}H_{20}N_2O \cdot HCl \cdot H_2O$ Theory C 61 82 H 7 46 N, 9 01 Found C. 62 13 H 7 86 N 9 24

EXAMPLE 8

5-pentanoyl-3-(1-methylpiperidin-4-yl)-1H-indole hydrochloride

Using 0 20 gm (0 66 mMol) N-methyl-N-methoxy-5-carboxamido-3-(1-methylpiperidin-4-yl)-1H-indole (Preparation II) and 1 66 mL (2 67 mMol) n-butyllithium gave 5-pentanoyl-3-(1-methylpiperidin-4-yl)-1H-indole which was converted to its hydrochloride salt 0 124 gm (63%) of the title compound were recovered as a tan solid which was crystallized from ethanol diethyl ether
m p =242-245°C
MS(m/e) 299(M^+)
Calculated for $C_{19}H_{26}N_2O \cdot HCl$ Theory C. 68 15. H, 8 13, N, 8 37 Found C, 67 89 H, 8 05, N 8 64

EXAMPLE 9

5-phenylacetyl-3-(1-methylpiperidin-4-yl)-1H-indole

Using 0 30 gm (1 0 mMol) N-methyl-N-methoxy-5-carboxamido-3-(1-methylpiperidin-4-yl)-1H-indole (Preparation II) and 2 5 mL (5 0 mMol) benzylmagnesium chloride gave 0 22 gm (66%) of the title compound as an off-white solid
m p =69°C
MS(m/e) 333(M^+)
IR 1662 cm^{-1}
Calculated for $C_{22}H_{24}N_2O$ Theory C 79 48 H 7 28 N 8 43 Found C, 79 68. H 7 47 N. 8 61

EXAMPLE 10

5-(4-methoxybenzoyl)-3-(1-methylpiperidin-4-yl)-1H-indole

To a solution of 0 35 mL (2 62 mMol) 4-methoxy-1-bromobenzene in 3 0 mL tetrahydrofuran at -78°C were added 1 83 mL (2 93 mMol) n-butyllithium and the reaction mixture stirred for 30 minutes at -78°C To this solution were then added 0 17 gm (0 56 mMol) N-methyl-N-methoxy-5-carboxamido-3-(1-methylpiperidin-4-yl)-1H-indole (Preparation II) in 2 0 mL tetrahydrofuran The reaction mixture was allowed to warm gradually to ambient and was then quenched with 2N sodium hydroxide The resulting mixture was extracted well with diethyl ether The ether extracts were then washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure The residue was purified by radial chromatography (2 mm silica), eluting with 10 1 dichloromethane methanol, to give 0 135 gm (72%) of the title compound as a light yellow solid
MS(m/e) 349(M^+)
Calculated for $C_{22}H_{24}N_2O_2$ Theory C 75 84 H. 6 94. N 8 04 Found C. 75 85. H. 7 11. N 8 06

The compounds of Examples 11-19 were prepared employing the method described in detail in Example 10

EXAMPLE 11

5-(4-fluorobenzoyl)-3-(1-methylpiperidin-4-yl)-1H-indole

Using 0 20 gm (0 66 mMol) N-methyl-N-methoxy-5-carboxamido-3-(1-methylpiperidin-4-yl)-1H-indole (Preparation II) and 0 36 mL (4 98 mMol) 4-fluoro-1-bromobenzene gave 0 158 gm (71%) of the title compound as an off-white solid m p =89°C
MS(m/e) 336(M^+)

EXAMPLE 12

5-(4-methylbenzoyl)-3-(1-methylpiperidin-4-yl)-1H-indole

Using 0 20 gm (0 66 mMol) N-methyl-N-methoxy-5-carboxamido-3-(1-methylpiperidin-4-yl)-1H-indole (Preparation II) and 0 41 mL (3 32 mMol) 4-methyl-1-bromobenzene gave 0 180 gm (79%) of the title compound as a yellow solid
m p =92°C

MS(m/e) 332(M^+)
Calculated for $C_{22}H_{24}N_2O$ Theory C 79 48 H 7 28 N 8 43 Found C 79 60 H 7 40 N 8 54

EXAMPLE 13

5-(4-trifluoromethylbenzoyl)-3-(1-methylpiperidin-4-yl)-1H-indole

Using 0 15 gm (0 50 mMol) N-methyl-N-methoxy-5-carboxamido-3-(1-methylpioeridin-4-yl)-1H-indole (Preparation II) and 0 35 mL (2 49 mMol) 4-trifluoromethyl-1-bromobenzene gave 0 122 gm (64%) of the title compound as a yellow solid m p =160-162°C
MS(m/e) 386(M^+)
Calculated for $C_{22}H_{21}N_2OF_3$ Theory C 68 38 H 5 48 N 7 25 Found C 68 54 H. 5 72 N 7 47

EXAMPLE 14

5-(4-trifluoromethoxybenzoyl)-3-(1-methylpiperidin-4-yl)-1H-indole

Using 0 17 gm (0 56 mMol) N-methyl-N-methoxy-5-carboxamido-3-(1-methylpiperidin-4-yl)-1H-indole (Preparation II) and 0 49 mL (3 32 mMol) 4-trifluoromethoxy-1-bromobenzene gave 0 157 gm (69%) of the title compound as a light yellow solid
m p =172-175°C
MS(m/e) 402(M^+)
Calculated for $C_{22}H_{21}N_2O_2F_3$ Theory C 65 66 H 5 26 N 6 96 Found C 65 86 H 5 45 N 7 20

EXAMPLE 15

5-(4-dimethylaminobenzoyl)-3-(1-methylpiperidin-4-yl)-1H-indole

Using 0 20 gm (0 66 mMol) N-methyl-N-methoxy-5-carboxamido-3-(1-methylpiperidin-4-yl)-1H-indole (Preparation II) and 0 80 gm (3 98 mMol) 4-dimethylamino-1-bromobenzene gave 0 159 gm (66%) of the title compound as a light yellow solid
m p =103-104°C
MS(m/e) 361(M^+)
Calculated for $C_{23}H_{27}N_3O{\cdot}0\,5\,H_2O$ Theory C, 74 56 H 7 62 N 11 34 Found C, 74 46 H 7 53 N 11 04

EXAMPLE 16

5-(2-naphthoyl)-3-(1-methylpiperidin-4-yl)-1H-indole

Using 0 20 gm (0 66 mMol) N-methyl-N-methoxy-5-carboxamido-3-(1-methylpiperidin-4-yl)-1H-indole (Preparation II) and 0 60 gm (3 32 mMol) 2-bromonaphthalene gave 0 178 gm (73%) of the title compound as a light yellow solid m p =92°C
MS(m/e) 368 (M^+)

EXAMPLE 17

5-(2-pyridinecarbonyl)-3-(1-methylpiperidin-4-yl)-1H-indole

Using 0 20 gm (0 66 mMol) N-methyl-N-methoxy-5-carboxamido-3-(1-methylpiperidin-4-yl)-1H-indole (Preparation II) and 0 32 mL (3 32 mMol) 2-bromopyridine gave 0 089 gm (42%) of the title compound as a light yellow solid
m p =90°C
MS(m/e) 319(M^+)

EXAMPLE 18

5-(N-phenylcarboxamido)-3-(1-methylpiperidin-4-yl)-1H-indole

Using 0 20 gm (0 66 mMol) N-methyl-N-methoxy-5-carboxamido-3-(1-methylpiperidin-4-yl)-1H-indole (Prepara-

tion II) and 0 30 mL (3 32 mMol) aniline gave 0 118 gm (53%) of the title compound as a light tan solid
m p =97°C
MS(m/e) 333(M^+)
Calculated for $C_{21}H_{23}N_3O$ 0 25 H_2O Theory C, 74 64, H 7 01 N, 12 43 Found C 74 29, H, 7 06 N 12 51

EXAMPLE 19

5-(N-benzylcarboxamido)-3-(1-methylpiperidin-4-yl)-1H-indole

Using 1 2 gm (4 0 mMol) N-methyl-N-methoxy-5-carboxamido-3-(1-methylpiperidin-4-yl)-1H-indole (Preparation III) and 2 2 mL (20 0 mMol) benzylamine gave 0 788 gm (57%) of the title compound as a white solid
m p =87°C
MS(m/e) 347(M^+)
Calculated for $C_{22}H_{25}N_3O$ Theory C, 76 05 H 7 25 N 12 09 Found C 76 06 H, 7 51 N 12 35

EXAMPLE 20

5-(4-chlorobenzoyl)-3-(1-methylpiperidin-4-yl)-1H-indole

To a suspension of 0 21 gm (1 05 mMol) potassium hydride in 5 0 mL tetrahydrofuran at 0°C were added a solution of 0 3 gm (1 0 mMol) 5-bromo-3-(1-methylpiperidin-4-yl)-1H-indole in 5 0 mL tetrahydrofuran and the solution stirred for about 30 minutes The resulting mixture was cooled to about -78°C and to it were added 1 47 mL (2 3 mMol) t-butyllithium which had been precooled to -78°C, via cannula After about 15 minutes, a solution of 1 0 gm (5 0 mMol) N-methyl-N-methoxy-4-chlorobenzamide (Preparation VII) in 3 0 mL tetrahydrofuran were added The reaction mixture was allowed to gradually warm to ambient and was then quenched with 2N sodium hydroxide The mixture extracted well with diethyl ether and the ether extracts were then washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure The residue was purified by radial chromatography (2 mm silica) eluting with 95 5 ethyl acetate methanol to give the title compound as a light yellow solid
m p =133°C
MS(m/e) 352(M^+)
Calculated for $C_{21}H_{21}N_2OCl$•0 5H_2O Theory C, 69 70, H, 6 13 N 7 74 Found C, 70 02, H 6 20, N, 7 93

EXAMPLE 21

5-methanesulfonylamino-3-(1-methyl-1 2,3,6-tetrahydropyridin-4-yl)-1H-indole

To a solution of 1 2 gm (21 4 mMol) potassium hydroxide in 12 mL methanol was added 1 0 gm (4 76 mMol) 5-methanesulfonylamino-1H-indole followed by 0 76 mL (6 2 mMol) 1-methyl-4-piperidone The homogeneous solution was heated to reflux for 18 hours under nitrogen The reaction mixture was then cooled and concentrated under reduced pressure The residue was dissolved in water and the pH of the solution adjusted from 14 to 8-9 by the addition of acid The precipitate that formed was filtered washed with water and dried under vacuum to give 1 3 gm (89 6%) of the title compound as a tan solid
m p =210-214°C
MS(m/e) 305(M^+)
Calculated for $C_{15}H_{19}N_3O_2S$ Theory C 58 99 H, 6 27, N 13 76 Found C, 59 00, H, 6 20 N, 13 74

The compounds of Examples 22-29 were prepared employing the procedure described in detail in Example 21

EXAMPLE 22

N-methyl-5-methanesulfonylamino-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 1 23 gm (5 5 mMol) N-methyl-5-methanesulfonylamino-1H-indole and 0 88 mL (7 1 mMol) 1-methyl-4-piperidone, 1 4 gm (80%) of the title compound were recovered as a tan, crystalline powder
m p =198-202°C
MS(m/e) 319(M^+)
Calculated for $C_{16}H_{21}N_3O_2S$ Theory C, 60 16 H, 6 63, N 13 16 Found C 60 30, H 6 76, N, 12 97

EXAMPLE 23

2-methyl-5-methanesulfonylamino-3-(1-methyl-1 2 3 6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 1 37 gm (6 1 mMol) 2-methyl-5-methanesulfonylamino-1H-indole and 0 98 mL (7 9 mMol) 1-methyl-4-piperidone 0 65 gm (33 3%) of the title compound were recovered as a yellow solid
m p =176-184°C
MS(m/e) 320(M+1)
Calculated for $C_{16}H_{21}N_3O_2S$ Theory C 60 16 H 6 63 N 13 16 Found C 60 39 H. 6 48. N. 13 10

EXAMPLE 24

5-ethanesulfonylamino-3-(1-methyl-1 2 3 6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 1 45 gm (6 5 mMol) 5-ethanesulfonylamino-1H-indole and 1 03 mL (6 4 mMol) 1-methyl-4-piperidone 1 23 gm (59 7%) of the title compound were recovered as pale orange crystals
m p =224-226°C
MS(m/e) 319(M^+)
Calculated for $C_{16}H_{21}N_3O_2S$ Theory C. 60 16 H 6 63 N 13 16 Found C 60 45 H 6 69 N 13 22

EXAMPLE 25

5-(N N-dimethylamino)sulfonylamino-3-(1-methyl-1 2 3 6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 1 17 gm (4 89 mMol) 5-(N,N-dimethylamino)sulfonylamino-1H-indole and 0 78 mL (6 4 mMol) 1-methyl-4-piperidone. 1 19 gm (72 6%) of the title compound were recovered as a pale yellow powder
m p =207-208°C
MS(m/e) 334(M^+)
Calculated for $C_{16}H_{22}N_4O_2S$ Theory C 57 46 H 6 63 N 16 75 Found C 57 69. H. 6 71 N 16 60

EXAMPLE 26

5-methanesulfonylamino-3-(1-ethyl-1 2,3 6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 1 50 gm (7 1 mMol) 5-methanesulfonylamino-1H-indole and 1 25 mL (9 3 mMol) 1-ethyl-4-piperidone, 1 34 gm (58 8%) of the title compound were recovered as a light yellow, crystalline powder
m p =218-219°C (dec)
MS(m/e) 320(M+1)
Calculated for $C_{16}H_{21}N_3O_2S$ Theory C 60 16. H, 6 63 N 13 16 Found C, 59 89 H 6 39 N 13 24

EXAMPLE 27

5-methanesulfonylamino-3-(1-propyl-1 2 3 6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 1 50 gm (7 1 mMol) 5-methanesulfonylamino-1H-indole and 1 4 mL (9 3 mMol) 1-propyl-4-piperidone 2 1 gm (88 2%) of the title compound were recovered as a yellow powder
m p =217-218 5°C (dec)
MS(m/e) 334(M+1)
Calculated for $C_{17}H_{23}N_3O_2S$ Theory C. 61 23. H, 6 95 N. 12 60 Found C 61 51 H, 7 23 N. 12 30

EXAMPLE 28

5-methanesulfonylamino-3-(1-isopropyl-1 2 3 6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 1 0 gm (4 76 mMol) 5-methanesulfonylamino-1H-indole and 0 873 gm (6 2 mMol) 1-isopropyl-4-piperidone 1 02 gm (64 2%) of the title compound were recovered as a tan powder
m p =211-213°C (dec)
MS(m/e) 333(M^+)

Calculated for $C_{17}H_{23}N_3O_2S$ Theory C 61 23 H 6 95 N 12 60 Found C. 60 95 H 6 87 N 12 60

EXAMPLE 29

5-methanesulfonylamino-3-(1-butyl-1 2 3 6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 1 0 gm (4 76 mMol) 5-methanesulfonylamino-1H-indole and 0 96 gm (6 2 mMol) 1-butyl-4-piperidone 1 4 gm (84 8%) of the title compound were recovered as a yellow powder
m p =202-204°C
MS(m/e) 347(M^+)
Calculated for $C_{18}H_{25}N_3O_2S$ Theory C, 62 22 H 7 25 N 12 09 Found C 62 10 H, 7 11 N, 12 28

EXAMPLE 30

5-methanesulfonylamino-3-(1-methylpiperidin-4-yl)-1H-indole oxalate

To a solution 0 815 gm (2 67 mMol) 5-methanesulfonylamino-3-(1-methyl-1 2.3.6-tetrahydropyridin-4-yl)-1H-indole in 125 mL methanol were added 0 815 gm 5% palladium on carbon The mixture was hydrogenated at ambient for 18 hours with an initial hydrogen pressure of 60 p s i The reaction mixture was filtered and the filtrate concentrated under reduced pressure The residual oil was purified by flash chromatography, eluting with 90 10 dichloromethane methanol Fractions shown to contain product were combined and concentrated under reduced pressure The residue was dissolved in methanol and to it were added oxalic acid The suspension was filtered to give 0 261 gm (25%) of the title compound
m p = 119 1°C
MS(m/e) 307(M^+)

EXAMPLE 31

5-(N-methyl)methanesulfonylamino-3-(1-methylpiperidin-4-yl)-1H-indole

Following the procedure described in detail in Example 30, 0 807 gm (2 53 mMol) 5-(N-methyl)methanesulfonylamino-3-(1-methyl-1 2.3 6-tetrahydropyridin-4-yl)-1H-indole (Example 22) was hydrogenated to give 0 075 gm (9 3%) of the title compound as a tan foam
MS(m/e) 322(M+1)
Calculated for $C_{16}H_{23}N_3O_2S$ Theory C, 59 79 H. 7 21 N 13 07 Found C, 59 62 H 7 33. N, 12 82

EXAMPLE 32

2-methyl-5-methanesulfonylamino-3-(1-methylpiperidin-4-yl)-1H-indole

To a solution of 0 45 gm (1 41 mMol) 2-methyl-5-methanesulfonylamino-3-(1,2.3.6-tetrahydropyridin-4-yl)-1H-indole (Example 23) in 125 mL methanol were added 0 11 gm 5% palladium on carbon and the reaction mixture hydrogenated at ambient temperature with an initial hydrogen pressure of 60 p s i After 18 hours the reaction mixture was filtered and the filtrate concentrated under reduced pressure to give a yellow oil The oil was purified by radial chromatography (2 mm silica gel). eluting with 100 5 0 5 dichloromethane methanol ammonium hydroxide, to give 0 21 gm of a yellow foam which was then precipitated from ethyl acetate/hexanes to give 0 18 gm (39 7%) of the title compound as a white powder m p =124-128°C
MS(m/e) 321(M^+)
Calculated for $C_{16}H_{23}N_3O_2S$ Theory C 59 79. H. 7 21 N, 13 07 Found C, 59 88 H, 7 24 N 13 33

The compounds of Examples 33-38 were prepared by the procedure described in detail in Example 32

EXAMPLE 33

5-ethanesulfonylamino-3-(1-methylpiperidin-4-yl)-1H-indole

0 70 gm (2 2 mMol) 5-ethanesulfonylamino-3-(1-methyl-1.2 3 6-tetrahydropyridin-4-yl)-1H-indole (Example 24) were hydrogenated to give 0 545 gm (77 4%) of the title compound as a white powder
m p =176-178°C

MS(m/e) 322(M+1)
Calculated for $C_{16}H_{23}N_3O_2S$ Theory C 59 79 H 7 21 N 13 07 Found C. 60 07 H 7 22 N 12 79

EXAMPLE 34

5-(N N-dimethylamino)sulfonylamino-3-(1-methylpiperidin-4-yl)-1H-indole

0 66 gm (2 0 mMol) 5-(N N-dimethylamino)sulfonylamino-3-(1-methyl-1 2 3 6-tetrahydropyridin-4-yl)-1H-indole (Example 25) were hydrogenated to give 0 333 gm (50 2%) of the title compound as an off-white powder
m p =179-181°C (dec)
MS(m/e) 336(M^+)
Calculated for $C_{16}H_{24}N_4O_2S$ Theory C 57 12 H 7 19. N 16 65 Found C. 57 38 H. 7 27 N 16 87

EXAMPLE 35

5-methanesulfonylamino-3-(1-ethylpiperidin-4-yl)-1H-indole

0 96 gm (3 0 mMol) 5-methanesulfonylamino-3-(1-ethyl-1 2 3 6-tetrahydropyridin-4-yl)-1H-indole (Example 26) were hydrogenated to give 0 531 gm (55 0%) of the title compound as an off-white powder
m p =179-181°C
MS(m/e) 321(M^+)
Calculated for $C_{16}H_{23}N_3O_2S$ Theory C 59 79 H 7 21. N 13 07 Found C 59 50 H. 7 11 N 12 81

EXAMPLE 36

5-methanesulfonylamino-3-(1-propylpiperidin-4-yl)-1H-indole

1 0 gm (3 0 mMol) 5-methanesulfonylamino-3-(1-propyl-1 2 3 6-tetrahydropyridin-4-yl)-1H-indole (Example 27) were hydrogenated to give 0 376 gm (37 2%) of the title compound as an off-white powder 0 376 gm (37 2%) of the title compound as an off-white powder
m p =87-90°C
MS(m/e) 335(M^+)
Calculated for $C_{17}H_{25}N_3O_2S$ Theory C. 60 87, H. 7 51, N 12 53 Found C 61 12 H 7 32 N. 12 70

EXAMPLE 37

5-methanesulfonylamino-3-(1-isopropylpiperidin-4-yl)-1H-indole

0 75 gm (2 25 mMol) 5-methanesulfonylamino-3-(1-isopropyl-1 2,3,6-tetrahydropyridin-4-yl)-1H-indole (Example 28) were hydrogenated to give 0 310 gm (41 1%) of the title compound as a white powder
m p =104-108°C
MS(m/e) 335(M^+)
Calculated for $C_{17}H_{25}N_3O_2S \cdot C_2H_2O_4$ Theory C 53 63 H 6 40 N. 9 87 Found C 53 38. H 6 34 N 9 66

EXAMPLE 38

5-methanesulfonylamino-3-(1-butylpiperidin-4-yl)-1H-indole

1 05 gm (3 02 mMol) 5-methanesulfonylamino-3-(1-butyl-1 2 3 6-tetrahydropyridin-4-yl)-1H-indole (Example 29) were hydrogenated to give 0 255 gm (24 0%) of the title compound as a tan foam
m p =78°C
MS(m/e) 349(M^+)
Calculated for $C_{18}H_{27}N_3O_2S$ Theory C 61 86 H 7 79. N 12 02 Found C 61 66 H. 7 74 N 11 87

EXAMPLE 39

5-benzenesulfonylamino-3-(1-methylpiperidin-4-yl)-1H-indole

To a solution of 2 00 gm (5 74 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole in 50 0 mL dichloromethane were added 1 63 gm (20 7 mMol) pyridine and the solution was cooled to 0°C To this cooled solution were then added dropwise a solution of 2 23 gm (12 6 mMol) benzenesulfonyl chloride in 50 mL dichloromethane The reaction mixture was allowed to warm gradually to ambient After 24 hours the reaction mixture was washed with 100 mL water and the remaining organics concentrated under reduced pressure The residue was suspended in water and the pH adjusted to 14 with sodium hydroxide The aqueous phase was then extracted well with dichloromethane The organic phase was washed sequentially with water and saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure The aqueous phases were combined and the pH adjusted to 10 by the addition of acid and extracted again with 3 1 chloroform isopropanol These organic extracts were combined and concentrated under reduced pressure The combined residues were subjected to flash chromtography eluting with a gradient system of 100 10 0 5 to 100 11 0 5 dichloromethane methanol ammonium hydroxide, giving 0 83 gm (39 1%) of the title compound as a white powder
m p =246-249°C (dec)
MS(m/e) 370(M+1)
Calculated for $C_{20}H_{23}N_3O_2S$ Theory C, 65 02 H 6 27 N. 11 37 Found C, 64 78 H 6 09. N. 11 44

EXAMPLE 40

5-(4-iodobenzenesulfonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Following the procedure described in detail in Example 39 0 791 gm (3 45 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 1 1 gm (3 62 mMol) 4-iodobenzenesulfonyl chloride were used to prepare 0 809 (47 3%) of the title compound as a white powder
m p >250°C
MS(m/e) 495(M+)
Calculated for $C_{20}H_{22}IN_3O_2S$ Theory C 48 49. H, 4 48. N. 8 48 Found: C 48 68. H. 4 47 N 8 26

EXAMPLE 41

5-(di(trifluoromethanesulfonyl))amino-3-(1-methylpiperidin-4-yl)-1H-indole hydrochloride

To a suspension of 1 00 gm (2 87 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole dihydrochloride in 100 mL dichloromethane were added 2 5 mL (14 3 mMol) diisopropylethylamine followed by 1 06 mL (6 3 mMol) trifluoromethanesulfonic anhydride After 20 minutes the reaction mixture was washed with water dried over sodium sulfate and concentrated under reduced pressure The residue was purified by flash chromatography, eluting with dichloromethane containing 15% methanol, to give 5-(di(trifluoromethanesulfonyl))amino-3-(1-methylpiperidin-4-yl)-1H-indole This material was converted to its hydrochloride salt and was crystallized from acetonitrile to give 0 34 gm (22 3%) of the title compound m p =175-185°C (dec)
MS(m/e) 493 (M^+)
Calculated for $C_{16}H_{17}N_3O_4S_2F_6 \cdot HCl$ Theory C, 36 27 H. 3 23. N. 7 93 Found: C, 36 48, H, 3 58, N, 7 85

EXAMPLE 42

5-(methoxycarbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

To a mixture of 10 mg (0 0437 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 15 0 mg (131 mMol) polyvinylpyridine in 3 0 mL dichloromethane were added 4 3 mg (0 0458 mMol) methyl chloroformate The reaction mixture was mixed for 18 hours at ambient temperature To this mixture were then added 170 mg (0 137 mMol) aminomethylated polystyrene and the reaction mixed for an additional 18 hours The reaction mixture was then filtered and the volatiles evaporated to give 10 2 mg (81%) of the title compound
MS(m/e) 287(M^+)
The compounds of Examples 43-50 were prepared by the procedure described in detail in Example 42

EXAMPLE 43

5-(ethoxycarbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 mg (0 0437 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 4 97 mg (0 0458 mMol) ethyl chloroformate 11 1 mg (84%) of the title compound were recovered
MS(m/e) 301(M+)

EXAMPLE 44

5-(propoxycarbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 mg (0 0437 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 5 62 mg (0 0458 mMol) propyl chloroformate 11 2 mg (81%) of the title compound were recovered
MS(m/e) 316(M+)

EXAMPLE 45

5-(allyloxycarbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 mg (0 0437 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 5 5 mg (0 0458 mMol) allyl chloroformate 9 7 mg (71%) of the title compound were recovered
MS(m/e) 314(M+)

EXAMPLE 46

5-((2-methoxyethyl)carbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 mg (0 0567 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 8 65 mg (0 062 mMol) 2-methoxyethyl chloroformate 10 25 mg (54%) of the title compound were recovered
MS(m/e) 332(M+)

EXAMPLE 47

5-(cyclopentyloxycarbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 mg (0 0567 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 9 27 mg (0 062 mMol) cyclopentyl chloroformate 18 1 mg (93%) of the title compound were recovered
MS(m/e) 342(M+)

EXAMPLE 48

5-(phenoxycarbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 mg (0 0437 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 7 2 mg (0 0458 mMol) phenyl chloroformate 13 9 mg (91%) of the title compound were recovered
MS(m/e) 350(M+)

EXAMPLE 49

5-(4-methoxyphenyl)oxycarbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 mg (0 0567 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 11 1 mg (0 062 mMol) 4-methoxyphenyl chloroformate 13 4 mg (63%) of the title compound were recovered
MS(m/e) 380(M+)

EXAMPLE 50

5-(4-chlorophenyl)oxycarbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 mg (0 0567 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 11 1 mg (0 062 mMol) 4-chlorophenyl chloroformate 18 1 mg (93%) of the title compound were recovered
MS(m/e)

EXAMPLE 51

N-methyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

To a solution of 2 0 gm (5 74 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole dihydrochloride mono-ethanolate and 5 0 mL (36 mMol) triethylamine in 100 mL dichloromethane were added 0 74 mL (12 6 mMol) methyl isocyanate The reaction mixture was stirred for 15 minutes and was then washed with 100 mL of water The remaining organics were dried over sodium sulfate and concentrated under reduced pressure The resultant residue was crystallized from acetonitrile to give 1 05 gm (64%) of the title compound MS(m/e) 287(M+1)
Calculated for $C_{16}H_{22}N_4O$ Theory C 69 11. H, 7 74 N 19 56 Found C. 69 37. H, 7 82 N, 19 67

EXAMPLE 52

N-phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea hydrochloride

To a solution of 2 0 gm (5 74 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole dihydrochloride mono-ethanolate and 5 0 mL (36 mMol) triethylamine in 100 mL dichloromethane were added 1 37 mL (12 6 mMol) phenyl isocyanate The reaction mixture was stirred for 15 minutes and was then washed with 100 mL of water The remaining organics were dried over sodium sulfate and concentrated under reduced pressure The resultant residue was crystallized from acetonitrile to give 1 40 gm (70%) N-phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea This material was dissolved in methanol and to it was added an equivalent of methanolic hydrogen chloride The solution was then concentrated under reduced pressure and the residual oil crystallized from ethanol to give the title compound m p =215-220°C
MS(m/e) 348(M^+)
Calculated for $C_{21}H_{24}N_4O{\cdot}HCl$ Theory C, 65 53. H, 6 55. N, 14 56 Found C, 65 27 H 6 43. N 14 35

EXAMPLE 53

N-ethyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

To a solution of 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole in 3 0 mL chloroform were added 9 3 mg (131 mMol) ethyl isocyanate The reaction was mixed for 48 hours and to it were then added 0 23 gm (131 mMol) aminomethylated polystyrene and the reaction mixed for an additional 18 hours The reaction mixture was then filtered and the volatiles evaporated to give 16 1 mg (82%) of the title compound
MS(m/e)

The compounds of Examples 54-75 were prepared by the procedure described in detail in Example 53

EXAMPLE 54

N-propyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 11 1 mg (0 131 mMol) propyl isocyanate, 5 8 mg of the title compound were recovered MS(m/e) 315(M^+)

EXAMPLE 55

N-allyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 11 1 mg (0 131 mMol) allyl isocyanate 19 6 mg (96%) of the title compound were recovered
MS(m/e) 313(M^+)

EXAMPLE 56

N-isopropyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 11 13 mg (0 131 mMol) isopropyl isocyanate 21 9 mg of the title compound were recovered MS(m/e) 315(M+)

EXAMPLE 57

N-n-butyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 11 1 mg (0 131 mMol) n-butyl isocyanate. 20 6 mg (96%) of the title compound were recovered
MS(m/e) 329(M+)

EXAMPLE 58

N-cyclchexyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 16 37 mg (0 131 mMol) cyclohexyl isocyanate 20 1 mg (87%) of the title compound were recovered
MS(m/e) 355(M+)

EXAMPLE 59

N-(1-ethoxycarbonyl-2-methylpropyl)-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 14 56 mg (0 0652 mMol) ethyl 2-isocyanato-3-methylbutyrate 25 0 mg (95%) of the title compound were recovered
MS(m/e) 401(M+)

EXAMPLE 60

N-(4-fluoro)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 9 9 mg (0 072 mMol) 4-fluorophenyl isocyanate 20 7 mg (86%) of the title compound were recovered
MS(m/e) 367(M+)

EXAMPLE 61

N-(4-chloro)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 11 0 mg (0 072 mMol) 4-chlorophenyl isocyanate 21 4 mg (86%) of the title compound were recovered
MS(m/e) 383(M+)

EXAMPLE 62

N-(4-methyl)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 9 6 mg (0 072 mMol) 4-methylphenyl isocyanate 23 7 mg (99%) of the title compound were recovered
MS(m/e) 363(M+)

EXAMPLE 63

N-(3-trifluoromethyl)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 16 0 mg (0 0852 mMol) 3-trifluoromethylphenyl isocyanate, 26 0 mg (95%) of the title compound were recovered
MS(m/e) 417(M^+)

EXAMPLE 64

N-(4-methoxy)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 10 7 mg (0 072 mMol) 4-methoxyphenyl isocyanate. 22 4 mg (91%) of the title compound were recovered
MS(m/e) 379(M^+)

EXAMPLE 65

N-(2-methoxy)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 10 7 mg (0 072 mMol) 2-methoxyphenyl isocyanate 21 7 mg (88%) of the title compound were recovered
MS(m/e) 379(M^+)

EXAMPLE 66

N-(4-methylthio)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 14 05 mg (0 0852 mMol) 4-methylthiophenyl isocyanate. 24 1 mg (93%) of the title compound were recovered
MS(m/e) 395 (M^+)

EXAMPLE 67

N-(3-acetyl)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 13 7 mg (0 0852 mMol) 3-acetylphenyl isocyanate, 25 0 mg (98%) of the title compound were recovered
MS(m/e) 391(M^+)

EXAMPLE 68

N-(4-butoxycarbonyl)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 15 8 mg (0 072 mMol) 4-carbobutoxyphenyl isocyanate 27 1 mg (92%) of the title compound were recovered
MS(m/e) 449(M^+)

EXAMPLE 69

N-(2-phenyl)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 16 6 mg (0 0852 mMol) 2-phenylphenyl isocyanate, 26 7 mg (96%) of the title compound were recovered
MS(m/e) 425 (M^+)

EXAMPLE 70

N-(4-phenyl)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 16 6 mg (0 0852 mMol) 4-phenylphenyl isocyanate 26 2 mg (95%) of the title compound were recovered
MS(m/e) 425 (M^+)

EXAMPLE 71

N-(2 3-dichloro)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 16 0 mg (0 0852 mMol) 2 3-dichlorophenyl isocyanate, 26 7 mg (98%) of the title compound were recovered
MS(m/e) 417(M^+)

EXAMPLE 72

N-benzyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 11 32 mg (0 0852 mMol) benzyl isocyanate 9 4 mg of the title compound were recovered
MS(m/e) 363(M^+)

EXAMPLE 73

N-phenethyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 12 51 mg (0 0852 mMol) 2-phenethyl isocyanate 15 8 mg (65%) of the title compound were recovered
MS(m/e) 377(M^+)

EXAMPLE 74

N-(α-methylbenzyl)-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 12 51 mg (0 0852 mMol) α-methylbenzyl isocyanate, 24 0 mg (97%) of the title compound were recovered
MS(m/e) 377(M^+)

EXAMPLE 75

N-(β-(ethoxycarbonyl)phenethyl)-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 16 6 mg (0 0852 mMol) ethyl 2-isocyanato-3-phenylpropionate , 28 0 mg (95%) of the title compound were recovered
MS(m/e) 449(M^+)

The compounds of Examples 76-79 were prepared at about 50°C by the procedure described in detail in Example 42

EXAMPLE 76

N,N-dimethyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 13 0 mg (056 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 6 4 mg (0 059 mMol) dimethyl carbamoyl chloride 13 2 mg (79%) of the title compound were recovered
MS(m/e) 301(M^+)

EXAMPLE 77

N N-diethyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 13 0 mg (056 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 8 0 mg (0 062 mMol) diethyl carbamoyl chloride 16 05 mg (86%) of the title compound were recovered
MS(m/e) 329(M^+)

EXAMPLE 78

N-methyl-N-phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)urea

Beginning with 13 0 mg (056 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 10 1 mg (0 059 mMol) N-methyl-N-phenyl carbamoyl chloride, 17 4 (86%) of the title compound were recovered
MS(m/e) 363(M^+)

EXAMPLE 79

5-(morpholin-1-yl)carbonylamino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 0 mg (056 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 8 9 mg (0 059 mMol) morpholine-1-carbonyl chloride 16 2 (85%) of the title compound were recovered
MS(m/e) 343 (M^+)

The compounds of Examples 80-86 were prepared by the procedure described in detail in Example 53

EXAMPLE 80

N-methyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)thiourea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 9 56 mg (0 098 mMol) methyl isothiocyanate, 17 0 mg (86%) of the title compound were recovered
MS(m/e) 303(M^+)

EXAMPLE 81

N-phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)thiourea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 13 26 mg (0 098 mMol) phenyl isothiocyanate, 16 8 mg (71%) of the title compound were recovered
MS(m/e) 365(M^+)

EXAMPLE 82

N-(4-methoxy)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)thiourea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 16 21 mg (0 098 mMol) 4-methoxyphenyl isothiocyanate 18 4 mg (71%) of the title compound were recovered
MS(m/e) 395(M^+)

EXAMPLE 83

N-(3-trifluoromethyl)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)thiourea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 19 94 mg (0 098 mMol) 3-trifluoromethylphenyl isothiocyanate 15 6 mg (55%) of the title compound were recovered
MS(m/e) 433(M^+)

EXAMPLE 84

N-(2-phenyl)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)thiourea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 20 73 mg (0 098 mMol) 2-biphenyl isothiocyanate 21 2 mg (74%) of the title compound were recovered
MS(m/e) 441(M^+)

EXAMPLE 85

N-(2,3-dichloro)phenyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)thiourea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 20 04 mg (0 098 mMol) 2 3-dichlorophenyl isothiocyanate 17 7 mg (62%) of the title compound were recovered
MS(m/e) 433(M^+)

EXAMPLE 86

N-benzyl-N'-(3-(1-methylpiperidin-4-yl)-1H-indol-5-yl)thiourea

Beginning with 15 0 mg (0655 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 14 63 mg (0 098 mMol) benzyl isothiocyanate 17 0 mg (86%) of the title compound were recovered
MS(m/e) 379(M^+)

EXAMPLE 87

5-phthalimido-3-(1-methylpiperidin-4-yl)-1H-indole oxalate

To a solution of 0 458 gm (2 0 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole in 8 0 mL dichloromethane were added 0 438 gm (2 0 mMol) N-carbethoxyphthalimide The reaction mixture was stirred 18 hours at ambient temperature at which time the solvent was removed under reduced pressure The residue was subjected to flash chromatography eluting with 100 20 0 5 dichloromethane methanol ammonium hydroxide giving 0 467 gm (65%) of 5-phthalimido-3-(1-methylpiperidin-4-yl)-1H-indole as a yellow foam The yellow foam was dissolved in a mixture of methanol ethyl acetate and to it was added an equivalent of oxalic acid The colorless precipitate which formed was recrystallized from methanol to give 0 267 gm of the title compound as colorless crystals
m p =224°C
MS(m/e) 359(M^+)
Calculated for $C_{22}H_{21}N_3O_2 \cdot C_2H_2O_4$ Theory C 64 13 H 5 16 N 9 35 Found C, 63 88, H 5 27 N, 9 51

EXAMPLE 88

5-(acetyl)amino-3-(1-methyl-1 2 3 6-tetrahydropyridin-4-yl)-1H-indole

To a solution of 1 0 gm (4 4 mMol) 5-amino-3-(1-methyl-1 2,3 6-tetrahydropyridin-4-yl)-1H-indole in 60 mL tetrahydrofuran were added 0 67 mL (4 8 mMol) triethylamine and the solution was cooled to 0°C To this solution were then added 0 32 mL (4 6 mMol) acetyl chloride and the reaction mixture was stirred at ambient temperature for 18 hours The reaction mixture was filtered and concentrated under reduced pressure to give a dark oil The oil was treated with water to give a black gum This residue was purified by radial chromatography (2 mm silica) eluting with 100 10 1 dichloromethane methanol ammonium hydroxide to give 0 20 gm (16 9%) of the title compound as a yellow solid
m p =186-189°C
MS(m/e) 269(M^+)
Calculated for $C_{16}H_{19}N_3O$ Theory C 71 35 H 7 11 N 15 60 Found C, 71 18 H 6 97 N 15 46

The compounds of Examples 89-110 are prepared by the procedure described in detail in Example 88

EXAMPLE 89

5-(propanoyl)amino-3-(1-methyl-1 2 3 6-tetrahydropyridin-4-yl)-1H-indol fumarate

Beginning with 1 0 gm (4 4 mMol) 5-amino-3-(1-methyl-1 2 3 6-tetrahydropyridin-4-yl)-1H-indole and 0 74 mL (5 3 mMol) propanoyl chloride, 0 287 gm (23%) of the title compound were recovered as a red powder
m p =170-173°C
MS(m/e) 283 (M^+)
Calculated for $C_{17}H_{21}N_3O \cdot C_4H_4O_4$ Theory C, 63 15 H, 6 31, N 10 52 Found C, 62 97, H, 6 04, N 10 66

EXAMPLE 90

5-(benzoyl)amino-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 1 13 gm (5 0 mMol) 5-amino-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole and 0 58 mL (5 0 mMol) benzoyl chloride 0 477 gm (28 9%) of the title compound were recovered as a light green solid
m p >250°C
MS(m/e) 331(M^+)
Calculated for $C_{21}H_{21}N_3O$ Theory C 76 11 H 6 39 N, 12 68 Found C 75 84, H, 6 22, N 12 41

EXAMPLE 91

5-(4-chlorobenzoyl)amino-3-(1-methyl-1 2,3 6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 1 13 gm (5 0 mMol) 5-amino-3-(1-methyl-1,2 3 6-tetrahydropyridin-4-yl)-1H-indole and 0 64 mL (5 0 mMol) 4-chlorobenzoyl chloride, 0 544 gm (29 9%) of the title compound were recovered as a tan solid
m p =224-226°C
MS(m/e) 365(M^+)
Calculated for $C_{21}H_{20}N_3OCl$ Theory C 68 94 H 5 51, N 11 48 Found C 68 75 H, 5 65 N, 11 63

EXAMPLE 92

5-(4-methoxybenzoyl)amino-3-(1-methyl-1 2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 1 13 gm (5 0 mMol) 5-amino-3-(1-methyl-1,2 3 6-tetrahydropyridin-4-yl)-1H-indole and 0 853 gm (5 0 mMol) 4-methoxybenzoyl chloride 0 367 gm (20 4%) of the title compound were recovered as a light yellow solid
m p =232°C (dec)
MS(m/e) 361(M^+)
Calculated for $C_{22}H_{23}N_3O_2$ Theory C, 73 11 H, 6 41, N, 11 63 Found C, 72 86, H, 6 39, N, 11 33

EXAMPLE 93

5-(2-chloro-4-fluorobenzoyl)amino-3-(1-methyl-1,2,3 6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 2 0 gm (8 8 mMol) 5-amino-3-(1-methyl-1,2 3 6-tetrahydropyridin-4-yl)-1H-indole and 1 9 gm (9 7 mMol) 2-chloro-4-fluorobenzoyl chloride, 0 67 gm (19 8%) of the title compound were recovered as a light yellow solid
m p =212-222°C
MS(m/e) 383(M^+)
Calculated for $C_{21}H_{19}N_3OClF$ Theory C, 65 71, H, 4 99; N, 10 95 Found C, 66 00, H, 5 10, N, 10 84

EXAMPLE 94

5-(4-fluorobenzoyl)amino-3-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 2 69 gm (11 1 mMol) 5-amino-3-(1-ethyl-1,2 3,6-tetrahydropyridin-4-yl)-1H-indole and 1 45 mL (12 3 mMol) 4-fluorobenzoyl chloride, 2 39 gm (59 0%) of the title compound were recovered as a burnt orange powder
m p =127-135°C (dec)
MS(m/e) 363(M^+)

Calculated for $C_{22}H_{22}N_3OF$ Theory C 72 71 H 6 10 N 11 56 Found C 72 42. H 6 14 N 11 33

EXAMPLE 95

5-(2-furoyl)amino-3-(1-methyl-1 2 3 6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 1 13 gm (5 0 mMol) 5-amino-3-(1-methyl-1 2 3 6-tetrahydropyridin-4-yl)-1H-indole and 0 52 mL (5 0 mMol) 2-furoyl chloride 0 129 gm (8 1%) of the title compound were recovered as a tan solid
m p =190°C (dec)
MS(m/e) 321(M^+)
Calculated for $C_{19}H_{19}N_3O_2$ Theory C 71 01 H, 5 96 N, 13 08 Found C, 71 26 H, 6 17 N 12 85

EXAMPLE 96

5-(2-thienoyl)amino-3-(1-methyl-1 2 3 6-tetrahydrop n-4-yl)-1H-indole

Beginning with 1 0 gm (4 4 mMol) 5-amino-3-(1 ethyl-1 2 3 6-tetrahydropyridin-4-yl)-1H-indole and 0 494 mL (4 6 mMol) 2-thiophenecarbonyl chloride 0 489 gm (33 0%) of the title compound were recovered as a bright yellow solid m p =229-233°C (dec)
MS(m/e) 337(M^+)
Calculated for $C_{19}H_{19}N_3OS$ Theory C 67 63 H, 5 67. N 12 45 Found C 67 44. H 5 70 N 12 22

EXAMPLE 97

5-(acetyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 2 00 gm (5 74 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole dihydrochloride ethanolate and 1 13 gm (25 8 mMol) acetyl chloride. 1 22 gm (78 3%) of the title compound were recovered as a white powder
m p =161-165°C (dec)
MS(m/e) 271(M^+)
Calculated for $C_{16}H_{21}N_3O$ Theory C 70 82 H 7 80 N, 15 48 Found C 70 52. H 7 83 N. 15 37

EXAMPLE 98

5-(propanoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole fumarate

Beginning with 0 945 gm (4 12 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 0 689 mL (4 94 mMol) propanoyl chloride. 1 3 gm (81 2%) of the title compound were recovered as a tan solid
m p =88-92°C (dec)
MS(m/e) 285(M^+)
Calculated for $C_{17}H_{23}N_3O \cdot C_4H_4O_4$ Theory C 62 83 H 6 78 N 10 47 Found C 62 61 H, 6 84 N 10 25

EXAMPLE 99

5-(trimethylacetyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 2 00 gm (5 74 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole dihydrochloride ethanolate and 1 78 gm (14 4 mMol) trimethylacetyl chloride 0 623 gm (34 6%) of the title compound were recovered as an off-white powder
m p =214-216°C (dec)
MS(m/e) 313(M^+)
Calculated for $C_{19}H_{27}N_3O$ Theory C 72 81 H 8 68 N 13 41 Found C, 72 56 H 8 73 N 13 28

EXAMPLE 100

5-(benzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole oxalate

Beginning with 0 545 gm (2 4 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 0 398 mL (2 85 mMol) ben-

zoyl chloride. 0 92 gm (90 5%) of the title compound were recovered as an off-white solid
m p =130°C
MS(m/e) 333(M^+)
Calculated for $C_{21}H_{23}N_3O \cdot C_2H_2O_4$ Theory C 65 24 H, 5 95. N, 9 92 Found C 64 98 H. 6 12. N 9 84

EXAMPLE 101

5-(4-fluorobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole fumarate

Beginning with 15 2 gm (66 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 7 8 mL (66 mMol) 4-fluorobenzoyl chloride, 13 01 gm (42 2%) of the title compound were recovered as an off-white solid
m p =139-140°C (dec)
MS(m/e). 351(M^+)
Calculated for $C_{21}H_{22}N_3OF \cdot C_4H_4O_4$ Theory C 64 23. H. 5 61. N -8 99 Found C. 63 96 H 5 65. N, 9 05

EXAMPLE 102

5-(2-chlorobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole fumarate

Beginning with 1 14 gm (5 0 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 0 63 mL (5 0 mMol) 2-chlorobenzoyl chloride. 0 406 gm (16 8%) of the title compound were recovered as colorless crystals
m p =209°C (dec)
MS(m/e). 367(M^+) Exact Mass Theory 368 1530. Found 368 1531

EXAMPLE 103

5-(3-chlorobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole fumarate

Beginning with 1 14 gm (5 0 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 0 62 mL (5 0 mMol) 3-chlorobenzoyl chloride, 0 942 gm (38 9%) of the title compound were recovered as a colorless solid
m p.=185°C (dec)
MS(m/e) 367(M^+)
Calculated for $C_{21}H_{22}N_3OCl \cdot C_4H_4O_4$ Theory C, 62 05. H 5 41 N, 8 68. Found. C. 61 77. H, 5 60. N, 8 61

EXAMPLE 104

5-(4-chlorobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole fumarate

Beginning with 1 14 gm (5 0 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 0 64 mL (5 0 mMol) 4-chlorobenzoyl chloride, 0 339 gm (14 0%) of the title compound were recovered as a colorless solid
m.p.=163°C (dec)
MS(m/e) 367(M^+)
Calculated for $C_{21}H_{22}N_3OCl \cdot C_4H_4O_4$. Theory C 62.05. H. 5 42. N, 8 68. Found C 61 92; H, 5 47. N, 8 52

EXAMPLE 105

5-(2-methoxybenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole fumarate

Beginning with 1 14 gm (5 0 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 0 74 mL (5 0 mMol) 2-methoxybenzoyl chloride. 0 569 gm (23 7%) of the title compound were recovered as an off-white solid
m p.=90°C (dec)
MS(m/e) 364(M^+)
Exact Mass Theory 364 2025 Found 364 2029

EXAMPLE 106

5-(3-methoxybenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole fumarate

Beginning with 1 14 gm (5 0 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 0 70 mL (5 0 mMol) 3-methoxybenzoyl chloride 0 653 gm (27 2%) of the title compound were recovered as an off-white solid
m p =152°C (dec)
MS(m/e) 364(M^+)
Calculated for $C_{22}H_{25}N_3O_2 \cdot C_4H_4O_4$ Theory C 65 12 H 6 10 N 8 76 Found C 64 85 H 6 38. N 8 48

EXAMPLE 107

5-(4-methoxybenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole fumarate

Beginning with 1 14 gm (5 0 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 0 853 gm (5 0 mMol) 4-methoxybenzoyl chloride 0 398 gm (16 6%) of the title compound were recovered as an off-white solid
m p =151°C (dec)
MS(m/e) 364(M^+)
Exact Mass Theory 364 2025 Found 364 2032

- EXAMPLE 108

5-(2-furoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole fumarate

Beginning with 1 14 gm (5 0 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 0 52 mL (5 0 mMol) 2-furoyl chloride 0 420 gm (19 1%) of the title compound were recovered as an off-white solid
m p =114°C (dec)
MS(m/e) 324(M^+)
Calculated for $C_{19}H_{21}N_3O_2 \cdot C_4H_4O_4$ Theory C 62 86 H 5 73 N 9 56 Found C 63 15 H 5 89 N, 9 64

EXAMPLE 109

5-(2-thienoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole oxalate

Beginning with 0 72 gm (3 14 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 0 525 mL (3 8 mMol) 2-thienoyl chloride 1 2 gm of the title compound were recovered as an off-white solid
m p =135°C (dec)
MS(m/e) 339(M^+)
Calculated for $C_{19}H_{21}N_3OS \cdot C_2H_2O_4$ Theory C, 58 61 H, 5 54 N 9 64 Found C 58 90, H, 5 41, N 9 69

EXAMPLE 110

5-(phenylacetyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole oxalate

Beginning with 2 00 gm (5 74 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole dihydrochloride ethanolate and 2 23 gm (14 4 mMol) phenylacetyl chloride, 0 80 gm of the title compound were recovered as a tan solid
m p <90°C
MS(m/e) 347(M^+)
Calculated for $C_{22}H_{25}N_3O \cdot C_2H_2O_4$ Theory C 65 89 H 6 22 N 9 60 Found C 65 68. H 6 29 N. 9 83

EXAMPLE 111

5-(fur-2-oyl)amino-3-(1-methyl-1,2,3 6-tetrahydropyridin-4-yl)-1H-indole

A Preparation of 5-(2-furoyl)amino-1H-indole

To a solution of 2 09 gm (15 8 mMol) 5-amino-1H-indole in 20 mL tetrahydrofuran were added 2 6 mL (18 97 mMol) triethylamine and the solution was cooled in an ice bath To the reaction mixture were then added dropwise 1 71 ml

(17 4 mMol) 2-furoyl chloride When this addition was complete the cooling bath was removed and the reaction mixture was stirred 1 5 hours at ambient temperature At this point the reaction was diluted with water and extracted well with ethyl acetate The organic solutions were combined and washed sequentially with water 2N sodium hydroxide. wat r and saturated aqueous sodium chloride The remaining organics were then dried over sodium sulfate and concentrated under reduced pressure to give a dark purple solid The solid was subjected to flash chromatography, eluting with a gradient of dichloromethane containing 0-2% methanol The recovered solid was crystallized from ethyl acetate to giv 1 8 gm (50 3%) of 5-(2-furoyl)amino-1H-indole as pale purple crystals

m p =181-182°C

MS(m/e) 227(M+1)

Calculated for $C_{13}H_{10}N_2O_2$ Theory C 69 02 H 4 46 N 12 38 Found C 68 79 H 4 52 N 12 25

B Condensation of substituted indole with 1-ethyl-4-piperidone

To a solution of 0 868 gm (15 5 mMol) potassium hydroxide in 8 mL methanol were added 1 0 gm (4 42 mMol) 5-(2-furoyl)amino-1H-indole and 0 774 mL 1-ethyl-4-piperidone and the solution was stirred at reflux for 18 hours The reaction mixture was cooled to ambient and then diluted with ice/water The resultant precipitate was collected and dried under vacuum This solid was purified by radial chromatography (2 mm silica), eluting with a gradient of dichloromethane containing 5-7 5% methanol and 0 5-1 0% ammonium hydroxide The product was then crystallized from ethyl acetate to give 0 715 gm (48 3%) of the title compound as a bright yellow powder

m p =120-122°C

MS(m/e) 336(M+1)

Calculated for $C_{20}H_{21}N_3O_2$ Theory C, 71 62, H, 6 31, N, 12 53 Found C, 71 51, H 6.33, N, 12 73

EXAMPLE 112

5-(2-furoyl)amino-3-(1-ethylpiperidin-4-yl)-1H-indole

To a solution of 0 780 gm (3 2 mMol) 5-amino-3-(1-ethylpiperidin-4-yl)-1H-indole in 10 mL tetrahydrofuran and 10 mL dimethylformamide were added 0 536 mL (3 85 mMol) triethylamine followed by the dropwise addition of 0 348 mL (3 5 mMol) 2-furoyl chloride After 18 hours the reaction mixture was cooled in an ice bath The reaction mixture was the partitioned between 100 mL ethyl acetate and 100 mL 2N sodium hydroxide The phases were separated and the aqueous extracted again with ethyl acetate Organic extracts were combined and washed sequentially with 2N sodium hydroxide, water and saturated aqueous sodium chloride The remaining organics were dried over sodium sulfate and concentrated under reduced pressure The residue was subjected to radial chromatography (2 mm silica), eluting with 100 10 1 dichloromethane methanol ammonium hydroxide Fractions containing product were combined and concentrated under reduced pressure The residue was crystallized from ethyl acetate/hexane to give 0 789 gm (73 1%) of the title compound as an off-white solid

m p =178-179°C

MS(m/e) 338(M+1)

Calculated for $C_{20}H_{23}N_3O_2$ Theory C, 71 19, H, 6 87, N, 12 45 Found C, 71 44, H, 7 09, N, 12 40

EXAMPLE 113

5-(4-fluorobenzoyl)amino-3-(1-ethylpiperidin-4-yl)-1H-indole fumarate

Following the procedure described in detail in Example 32 1 14 gm (3 14 mMol) 5-(4-fluorobenzoyl)amino-3-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole were hydrogenated to give 0 527 gm (34 8%) of the title compound as a tan powder

m p.=152-155°C

MS(m/e) 366(M+1)

Calculated for $C_{22}H_{24}N_3OF \cdot C_4H_4O_4$ Theory C, 64 85, H, 5 86 N 8 73 Found C 65 15 H, 5 95 N, 8 95

EXAMPLE 114

5-(2-chloro-4-fluorobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

To a solution of 0 40 gm (1 04 mMol) 5-(2-chloro-4-fluorobenzoyl)amino-3-(1-methyl-1 2,3,6-tetrahydropyridin-4-yl)-1H-indole in 5 2 mL trifluoroacetic acid were added 0 208 mL (1 3 mMol) triethylsilane and the reaction mixture

was stirred at ambient After 2 hours the reaction mixture was concentrated under reduced pressure To the residue was added 2N sodium hydroxide and the aqueous was extracted with dichloromethane The combined organic extracts were washed with 2N sodium hydroxide dried over sodium sulfate and then concentrated under reduced pressure to give an orange foam The foam was subjected to radial chromatography (2 mm silica), eluting with 100 10 1 dichloromethane methanol ammonium hydroxide The residue was crystallized from ethyl acetate/hexanes to give 0 27 gm (67 3%) of the title compound as a burnt orange powder
MS(m/e) 385(M+)

The compounds of Examples 115-124 were prepared by the procedure described in detail in Example 42

EXAMPLE 115

5-(methoxyacetyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 mg (0 056 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 6 5 mg (0 059 mMol) methoxy-acetyl chloride 14 2 mg (84%) of the title compound were recovered
MS(m/e) 302(M^+)

EXAMPLE 116

5-((2-thienyl)acetyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 mg (0 056 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 9 6 mg (0 059 mMol) (2-thiophene)acetyl chloride 14 1 mg (72%) of the title compound were recovered
MS(m/e) 354(M^+)

EXAMPLE 117

5-(3-(methoxycarbonyl)propanoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 mg (0 056 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 9 0 mg (0 059 mMol) (3-methoxycarbonyl)propanoyl chloride 14 1 mg (75%) of the title compound were recovered
MS(m/e) 344(M^+)

EXAMPLE 118

5-(2-fluorobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 mg (0 0437 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 5 4 µL (0 0458 mMol) 2-fluorobenzoyl chloride, 12 2 mg (80%) of the title compound were recovered
MS(m/e) 351(M^+)

EXAMPLE 119

5-(2-methylbenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 mg (0 0437 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 6 0 µL (0 0458 mMol) 2-methylbenzoyl chloride 14 3 mg (95%) of the title compound were recovered
MS(m/e) 348(M+1)

EXAMPLE 120

5-(3-methylbenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 mg (0 056 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 9 2 mg (0 059 mMol) 3-methylbenzoyl chloride, 17 1 mg (88%) of the title compound were recovered
MS(m/e) 348(M^+)

EXAMPLE 121

5-(2-trifluoromethylbenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 mg (0 056 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 13 0 mg (0 062 mMol) 2-trifluoromethylbenzoyl chloride. 20 3 mg (89%) of the title compound were recovered
MS(m/e) 401(M^+)

EXAMPLE 122

5-(3,4-dichlorobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 mg (0 0437 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 9 6 mg (0 0458 mMol) 3 4-dichlorobenzoyl chloride 14 4 mg (82%) of the title compound were recovered
MS(m/e) 401(M^+)

EXAMPLE 123

5-(2 4-dichlorobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 mg (0 0437 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 6 4 µL (0 0458 mMol) 2,4-dichlorobenzoyl chloride, 12 2 mg (80%) of the title compound were recovered
MS(m/e) 401(M^+)

EXAMPLE 124

5-(isoxazol-5-oyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 13 mg (0 056 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 8 21 mg (0 062 mMol) isoxazole-5-carbonyl chloride, 10 4 mg (57%) of the title compound were recovered
MS(m/e) 325(M^+)

EXAMPLE 125

Alternate Synthesis of 5-(2-thienoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole oxalate

To a solution of 0 615 gm (4 8 mMol) 2-thienoic acid in 10 mL dichloromethane were added 0 778 gm (4 8 mMol) N N-carbonyldiimidazole in 2 mL dichloromethane After 1 5 hour a solution of 1 0 gm (4 4 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole in 15 mL dichloromethane was added and the reaction mixture stirred for 18 hours at ambient The reaction mixture was washed sequentially with 1N sodium hydroxide, water and saturated aqueous sodium chloride The remaining organics were dried over sodium sulfate and the volatiles removed under reduced pressure The residual brown foam was subjected to radial chromatography (2 mm silica), eluting with a gradient of dichloromethane containing 5-7 5% methanol and 0 5% ammonium hydroxide Fractions shown to contain product were combined and concentrated under reduced pressure This material was dissolved in ethyl acetate/ethanol and was treated with oxalic acid to give 0 20 gm (10 7%) of the title compound as a tan solid
m p =160°C
MS(m/e) 339(M^+)
Calculated for $C_{19}H_{21}N_3OS \cdot C_2H_2O_4$ Theory C, 58 73 H, 5 40, N, 9 78 Found C, 58 61 H, 5 54, N 9 64

General procedure for the coupling of carboxylic acids with 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole

To a suspension of 4-5 equivalents of polymer bound 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (Desai, *et al*, *Tetrahedron Letters*, **34**(48), 7685 (1993)) in chloroform are added 1 equivalent of 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 2-3 equivalents of the carboxylic acid The reaction is agitated until the reaction is complete, heat may be applied if necessary The resin is removed by filtration and the product isolated by evaporation of solvent This procedure is illustrated by Examples 126-178

EXAMPLE 126

5-(1-propanoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12.0 mg (0.05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 8 µL (0.1 mMol) 1-propanoic acid 13.0 mg (91%) of the title compound were recovered
MS(m/e) 286(M+1)

EXAMPLE 127

5-(2-methylpropanoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12.0 mg (0.05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 8.8 mg (0.10 mMol) isobutyric acid 11.8 mg (79%) of the title compound were recovered
MS(m/e) 300(M+1)

EXAMPLE 128

5-(3-methylbutanoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12.0 mg (0.05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 10.0 mg (0.10 mMol) isovaleric acid 17.0 mg (100+%) of the title compound were recovered
MS(m/e) 314(M^-)

EXAMPLE 129

5-(1-pentanoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12.0 mg (0.05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 10.0 mg (0.10 mMol) pentanoic acid 12.8 mg (82%) of the title compound were recovered
MS(m/e) 314(M+1)

EXAMPLE 130

5-(ethoxyacetyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12.0 mg (0.05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 11.0 µL (0.10 mMol) ethoxyacetic acid 15.2 mg (97%) of the title compound were recovered
MS(m/e) 316(M+1)

EXAMPLE 131

5-(phenoxyacetyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12.0 mg (0.05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 15.0 mg (0.10 mMol) phenxoyacetic acid 9.4 mg (52%) of the title compound were recovered
MS(m/e) 364(M+1)

EXAMPLE 132

5-(diphenylacetyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12.0 mg (0.05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 21.0 mg (0.10 mMol) diphenylacetic acid 14.0 mg (66%) of the title compound were recovered
MS(m/e) 424(M+1)

EXAMPLE 133

5-(cinnamoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12 0 mg (0 05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 15 0 mg (0 10 mMol) cinnamic acid 7 2 mg (40%) of the title compound were recovered
MS(m/e) 360(M+1)

EXAMPLE 134

5-(cyclopropanecarbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12 0 mg (0 05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 9 0 µL (0 10 mMol) cyclopropanecarboxylic acid, 11 4 mg (77%) of the title compound were recovered
MS(m/e) 298(M+1)

EXAMPLE 135

5-(cyclobutanecarbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12 0 mg (0 05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 15 0 mg (0 10 mMol) cyclobutanecarboxylic acid, 15 0 mg (96%) of the title compound were recovered
MS(m/e) 312(M+1)

EXAMPLE 136

5-(cyclopentanecarbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12 0 mg (0 05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 11 0 mg (0 10 mMol) cyclopentanecarboxylic acid, 16 4 mg (100+%) of the title compound were recovered
MS(m/e) 326(M+1)

EXAMPLE 137

5-(cyclohexanecarbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12 0 mg (0 05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 13 0 mg (0 10 mMol) cyclohexanecarboxylic acid 20 6 mg (100+%) of the title compound were recovered
MS(m/e) 340(M+1)

EXAMPLE 138

5-(1,2,3,4-tetrahydronaphth-1-oyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12 0 mg (0 05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole with 16 2 mg (0 10 mMol) 1 2,3,4-tetrahydro-1-naphthoic acid at 70°C, 16 2 mg (84%) of the title compound were recovered
MS(m/e) 388(M+1)

EXAMPLE 139

5-(3-fluorobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12 0 mg (0 05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 21 0 mg (0 15 mMol) 3-fluorobenzoic acid, 11 8 mg (67%) of the title compound were recovered
MS(m/e) 352(M+1)

EXAMPLE 140

5-(4-bromobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 20.0 mg (0.067 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 52.0 mg (0.131 mMol) 4-bromobenzoic acid 27.3 mg (75.8%) of the title compound were recovered
MS(m/e) 413(M^+)

EXAMPLE 141

5-(4-iodobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10.0 mg (0.044 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 32.0 mg (0.131 mMol) 4-iodobenzoic acid 12.0 mg (60%) of the title compound were recovered
MS(m/e) 459(M^+)

EXAMPLE 142

5-(3-iodobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10.0 mg (0.044 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 32.0 mg (0.131 mMol) 3-iodobenzoic acid 15.9 mg (80%) of the title compound were recovered
MS(m/e) 459(M^+)

EXAMPLE 143

5-(4-methylbenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Reacting 12.0 mg (0.05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole with 14.0 mg (0.10 mMol)-4-methylbenzoic acid at 70°C. 12.0 mg (69%) of the title compound were recovered
MS(m/e) 348(M+1)

EXAMPLE 144

5-(4-hexyloxybenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10.0 mg (0.044 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 30.0 mg (0.131 mMol) 4-hexyloxybenzoic acid, 16.8 mg (89%) of the title compound were recovered
MS(m/e) 434(M+1)

EXAMPLE 145

5-(4-trifluoromethylbenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12.0 mg (0.05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 29.0 mg (0.15 mMol) 4-trifluoromethylbenzoic acid 11.6 mg (58%) of the title compound were recovered
MS(m/e) 402(M+1)

EXAMPLE 146

5-(3-trifluoromethylbenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 7.0 mg (0.03 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 17.1 mg (0.09 mMol) 3-trifluoromethylbenzoic acid 8.7 mg (72%) of the title compound were recovered
MS(m/e) 403(M+2)

EXAMPLE 147

5-(4-cyanobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 20 0 mg (0 067 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 38 0 mg (0 131 mMol) 4-cyanobenzoic acid 13 5 mg (43 1%) of the title compound were recovered
MS(m/e) 359(M+1)

EXAMPLE 148

5-(4-nitrobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 20 0 mg (0 067 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 44 0 mg (0 131 mMol) 4-nitrobenzoic acid, 13 8 mg (41 8%) of the title compound were recovered
MS(m/e) 379(M+1)

EXAMPLE 149

5-(4-(methylthio)benzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 20 0 mg (0 087 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 44 0 mg (0 131 mMol) 4-(methylthio)benzoic acid, 18 9 mg (57 1%) of the title compound were recovered
MS(m/e) 380(M+1)

EXAMPLE 150

5-(3-(dimethylamino)benzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Reacting 12 0 mg (0 05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole with 17 0 mg (0 10 mMol) 3-(dimethylamino)benzoic acid at 70°C, 12 4 mg (66%) of the title compound were recovered
MS(m/e) 377(M+1)

EXAMPLE 151

5-(4-phenylbenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Reacting 12 0 mg (0 05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole with 20 0 mg (0 10 mMol) 4-phenylbenzoic acid at 70°C, 10 0 mg (49%) of the title compound were recovered
MS(m/e) 410(M+1)

EXAMPLE 152

5-(4-(acetyl)benzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 20 0 mg (0 087 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 44 0 mg (0 131 mMol) 4-(acetyl)benzoic acid, 16 5 mg (50 5%) of the title compound were recovered
MS(m/e) 376(M+1)

EXAMPLE 153

5-(4-(benzoyl)benzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 0 mg (0 044 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 30 0 mg (0 131 mMol) 4-(benzoyl)benzoic acid, 14 4 mg (75%) of the title compound were recovered
MS(m/e) 438(M+1)

EXAMPLE 154

5-(4-(methanesulfonyl)benzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 7 0 mg (0 03 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 18 0 mg (0 09 mMol) 4-(methanesulfonyl)benzoic acid 7 2 mg of the title compound were recovered
MS(m/e) 411(M^+)

EXAMPLE 155

5-(3,5-dichlorobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 7 0 mg (0 03 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 17 2 mg (0 09 mMol) 3 5-dichlorobenzoic acid 10 3 mg of the title compound were recovered
MS(m/e) 402(M^+)

EXAMPLE 156

5-(3 4-dimethylbenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 0 mg (0 044 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 19 6 mg (0 131 mMol) 3 4-dimethylbenzoic acid 12 0 mg (76%) of the title compound were recovered
MS(m/e) 362(M+1)

EXAMPLE 157

5-(3 5-dimethylbenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 0 mg (0 044 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 19 6 mg (0 131 mMol) 3,5-dimethylbenzoic acid, 15 0 mg (95%) of the title compound were recovered
MS(m/e) 362(M+1)

EXAMPLE 158

5-(2,3-dimethoxybenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 7 0 mg (0 03 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 16 4 mg (0 09 mMol) 2,3-dimethoxybenzoic acid 11 4 mg (97%) of the title compound were recovered
MS(m/e) 394(M+1)

EXAMPLE 159

5-(3-nitro-4-chlorobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 0 mg (0 044 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 26 4 mg (0 131 mMol) 3-nitro-4-chlorobenzoic acid 11 4 mg (63 3%) of the title compound were recovered
MS(m/e) 412(M^+)

EXAMPLE 160

5-(3,4,5-trimethoxybenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 0 mg (0 044 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 27 8 mg (0 131 mMol) 3,4 5-trimethoxybenzoic acid 13 8 mg (75%) of the title compound were recovered
MS(m/e) 424(M+1)

EXAMPLE 161

5-(3 5-(di-t-butyl)-4-hydroxybenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 0 mg (0 044 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 32 8 mg (0 131 mMol) 3 5-di(t-butyl)-4-hydroxybenzoic acid 15 0 mg (75%) of the title compound were recovered
MS(m/e) 462(M+1)

EXAMPLE 162

5-(pyridine-2-carbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12 0 mg (0 05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 19 0 mg (0 15 mMol) pyridine-2-carboxylic acid 14 2 mg (85%) of the title compound were recovered
MS(m/e) 335(M+1)

EXAMPLE 163

5-(pyridine-3-carbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 7 0 mg (0 03 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 11 1 mg (0 09 mMol) pyridine-3-carboxylic acid, 7 4 mg of the title compound were recovered
MS(m/e) 335(M+1)

EXAMPLE 164

5-(pyridine-4-carbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 7 0 mg (0 03 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 11 1 mg (0 09 mMol) pyridine-4-carboxylic acid 7 0 mg of the title compound were recovered
MS(m/e) 335(M+1)

EXAMPLE 165

5-(6-chloropyridine-3-carbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 7 0 mg (0 03 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 14 2 mg (0 09 mMol) 6-chloropyridine-3-carboxylic acid, 4 4 mg (40%) of the title compound were recovered
MS(m/e) 369(M+1)

EXAMPLE 166

5-(2-quinolinoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12 0 mg (0 05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 17 0 mg (0 10 mMol) 2-quinaldic acid 17 6 mg (92%) of the title compound were recovered
MS(m/e). 385(M+1)

EXAMPLE 167

5-(pyrazine-2-carbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 20 0 mg (0 087 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 32 mg (0 131 mMol) pyrazine-2-carboxylic acid 6 9 mg (24%) of the title compound were recovered
MS(m/e) 336(M+1)

EXAMPLE 168

5-(2-pyrroyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 0 mg (0 044 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 21 1 mg (0 131 mMol) pyrrole-2-carboxylic acid 12 6 mg (78%) of the title compound were recovered
MS(m/e) 323(M+1)

EXAMPLE 169

5-(N-methyl-2-pyrroyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12 0 mg (0 05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 19 0 mg (0 15 mMol) N-methylpyrrole-2-carboxylic acid. 18 0 mg (100+%) of the title compound were recovered
MS(m/e) 337(M+1)

EXAMPLE 170

5-(2-methyl-3-furoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 7 0 mg (0 03 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 11 3 mg (0 09 mMol) 2-methyl-3-furoic acid 0 4 mg (4%) of the title compound were recovered
MS(m/e) 338(M+1)

EXAMPLE 171

5-(3-furoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12 0 mg (0 05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 17 0 mg (0 15 mMol) 3-furoic acid 13 8 mg (85%) of the title compound were recovered
MS(m/e) 324(M+1)

EXAMPLE 172

5-(5-methyl-2-furoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 7 0 mg (0 03 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 11 3 mg (0 09 mMol) 5-methyl-2-furoic acid 8 8 mg (87%) of the title compound were recovered
MS(m/e) 338(M+1)

EXAMPLE 173

5-(5-bromo-2-furoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 10 0 mg (0 044 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 25 0 mg (0 131 mMol) 5-bromo-2-furoic acid 8 4 mg (48%) of the title compound were recovered
MS(m/e) 403(M^+)

EXAMPLE 174

5-(benzofuran-2-carbonyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12 0 mg (0 05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 24 0 mg (0 15 mMol) benzofuran-2-carboxylic acid 15 6 mg (84%) of the title compound were recovered
MS(m/e) 374(M+1)

EXAMPLE 175

5-(3-thienoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 7 0 mg (0 03 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indol and 11 5 mg (0 09 mMol) 3-thienoic acid 9 4 mg (92%) of the title compound were recovered
MS(m/e) 340(M+1)

EXAMPLE 176

5-(3-methyl-2-thienoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 7 0 mg (0 03 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 12 8 mg (0 09 mMol) 3-methyl-2-thienoic acid 9 6 mg (90%) of the title compound were recovered
MS(m/e) 354(M+1)

EXAMPLE 177

5-(5-methyl-2-thienoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 12 0 mg (0 05 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 21 0 mg (0 10 mMol) 5-methyl-2-thienoic acid, 13 0 mg (74%) of the title compound were recovered
MS(m/e) 354(M+1)

EXAMPLE 178

5-(4-methoxy-3-thienoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

Beginning with 7 0 mg (0 03 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole and 14 2 mg (0 09 mMol) 4-methoxy-3-thienoic acid, 12 1 mg of the title compound were recovered
MS(m/e) 369(M^+)

EXAMPLE 179

5-(1-naphthoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole hydrochloride

To a suspension of 1 2 gm (5 2 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole in 50 mL tetrahydrofuran were added 0 946 mL (6 3 mMol) 1-naphthoyl chloride dropwise After 18 hours the reaction mixture was filtered The recovered filtrate was dissolved in 10 mL dimethylformamide to which were added 1 5 mL (10 5 mMol) triethylamine followed by 0 8 mL (5 3 mMol) 1-naphthoyl chloride After 18 hours the reaction mixture was partitioned between ethyl acetate and 1N sodium hydroxide The phases were separated and the aqueous extracted again with ethyl acetate The combined ethyl acetate extracts were then washed sequentially with 1N sodium hydroxide, water and saturated aqueous sodium chloride The remaining organics were dried over sodium sulfate and concentrated under reduced pressure The residue was subjected to flash chromatography, eluting with 100 10 1 dichloromethane methanol ammonium hydroxide Fractions shown to contain product were combined and concentrated under reduced pressure The residue was taken up in ethanol and treated with ethanolic hydrogen chloride The solution was concentrated under reduced pressure and the residue crystallized from ethylacetate/ethanol to give 1 28 gm (58 2%) of the title compound as a tan powder
m p =193-203°C
MS(m/e) 384(M+1)
Calculated for $C_{25}H_{25}N_3O \cdot HCl \cdot 0\ 3\ CH_3CO_2CH_2CH_3$ Theory C, 70 50 H, 6 41 N, 9 41 Cl, 7 94 Found C, 70 10 H 6 41 N, 9 41, Cl, 8 34

EXAMPLE 180

5-(2-naphthoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

To a solution of 0 989 gm (4 31 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole in 20 mL tetrahydrofuran and

10 mL dimethylformamide were added 0 721 mL (5 2 mMol) triethylamine followed by 0 904 gm (4 74 mMol) 2-naphthoyl chloride After 18 hours the reaction mixture was cooled in an ice bath and then diluted with 100 mL ethyl acetate followed by 50 mL 2N sodium hydroxide The phases were separated and the aqueous extracted with ethyl acetate The organic extracts were combined then washed sequentially with 2N sodium hydroxide water and saturated aqueous sodium chloride The remaining organics were dried over sodium sulfate and concentrated under reduced pressure The residue was subjected to flash chromatography eluting with 100 10 1 dichloromethane methanol ammonium hydroxide Fractions shown to contain product were combined and concentrated under reduced pressure The residue was precipitated from ethyl acetate/hexane to give 1 355 gm (82 1%) of the title compound as a tan powder
m p =153-155 5°C
MS(m/e) 383(M^+)
Calculated for $C_{25}H_{25}N_3O$ Theory C, 78 30. H 6 57 N. 10 96 Found C 78 24 H. 6 63 N 11 10

EXAMPLE 181

Alternate Synthesis of 5-(2-chloro-4-fluorobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole

To a suspension of 0 804 gm (3 5 mMol) 5-amino-3-(1-methylpiperidin-4-yl)-1H-indole in 10 mL tetrahydrofuran and 5 0 mL dimethylformamide were added 0 586 mL (4 2 mMol) triethylamine followed by a solution of 0 744 gm (3 86 mMol) 2-chloro-4-fluorobenzoyl chloride in 5 mL tetrahydrofuran After 18 hours the reaction mixture was diluted with ethyl acetate followed by 2N sodium hydroxide The phases were separated and the aqueous extracted with ethyl acetate The organic extracts were combined then washed sequentially with 2N sodium hydroxide water and saturated aqueous sodium chloride The remaining organics were dried over sodium sulfate and concentrated under reduced pressure The residue was subjected to flash chromatography eluting with 100 10 1 dichloromethane methanol ammonium hydroxide Fractions shown to contain product were combined and concentrated under reduced pressure The residue was precipitated from ethyl acetate to give 0 921 gm (68 2%) of the title compound as a light pink powder
m p =159-162°C
MS(m/e) 385(M^+)
Calculated for $C_{21}H_{21}N_3OClF$ Theory C 65 37. H, 5 49 N 10 89 Found C 65 15 H 5 55 N 10 74

EXAMPLE 182

Alternate Synthesis of 5-(4-fluorobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1H-indole fumarate

A Preparation of 5-(4-fluorobenzoyl)amino-1H-indole

To a solution of 3 96 gm (30 0 mMol) 5-amino-1H-indole in 150 mL tetrahydrofuran were added 5 6 mL triethylamine followed by a solution of 5 2 gm (33 0 mMol) 4-fluorobenzoyl chloride in 30 mL tetrahydrofuran After 18 hours the reaction mixture was poured into water made basic with sodium hydroxide solution and extracted with dichloromethane The organic extracts were combined, dried over sodium sulfate and concentrated under reduced pressure to give a purple solid This residue was recrystallized from ethyl acetate/hexane to give 6 37 gm (84%) 5-(4-fluoro-benzoyl) amino-1H-indole as brown crystals in two crops
m p =205-207°C
MS(m/e) 254(M^+)
Calculated for $C_{15}H_{11}N_2OF$ Theory C 70 86 H. 4 36 N. 11 02 Found C 70 64 H 4 43 N 10 73

B Preparation of 5-(4-fluorobenzoyl)amino-3-(1-methyl-1 2 3,6-tetrahydropyridin-4-yl)-1H-indole

A solution of 2 54 gm (10 mMol) 5-(4-fluorobenzoyl)-amino-1H-indole and 1 7 gm (15 0 mMol) 1-methyl-4-piperidone in 20 mL 10% methanolic potassium hydroxide was heated to reflux for 3 5 hours and then allowed to stir without heating After 18 hours the resultant suspension was filtered the solid washed with methanol and then dried under reduced pressure to give 2 30 gm (65 8%) 5-(4-fluorobenzoyl)-amino-3-(1-methyl-1 2 3 6-tetrahydropyridin-4-yl)-1H-indole as a tan powder
m p =187 5-189 5°C
MS(m/e) 349(M^+)
Calculated for $C_{21}H_{20}N_3OF$ Theory C 72 19 H 5 77 N 12 03 Found C 72 36 H 5 87 N 12 01

C Hydrogenation of 5-(4-fluorobenzoyl)amino-3-(1-methyl-1 2 3 6-tetrahydropyridin-4-yl)-1H-indole

To a solution of 0 84 gm (2 4 mMol) 5-(4-fluorobenzoyl)-amino-3-(1-methyl-1 2 3,6-tetrahydropyridin-4-yl)-1H-indole in 100 mL methanol were added 0 25 gm 5% palladium on carbon and the mixture stirred under a hydrogen atmosphere maintained with a hydrogen filled balloon After 15 hours the mixture was filtered and the filtrate concentrated under reduced pressure The residual light yellow glass was then subjected to Florisil™ chromatography, eluting with 4 1 dichloromethane methanol containing a trace of ammonium hydroxide Fractions shown to contain product were combined and concentrated under reduced pressure The residue was dissolved in ethyl acetate and this solution treated with a saturated solution of fumaric acid in methanol The solvent was decanted from the precipitate which was recrystallized from ethyl acetate/methanol to give 0 377 gm (33 6%) of the title compound as colorless needles in two crops

m p =155-158°C (dec)

MS(m/e) 351(M^+)

Calculated for $C_{21}H_{22}N_3OF \cdot C_4H_4O_4$ Theory C 64 23 H. 5 61. N. 8 99 Found C 64 50, H, 5 58. N, 8 78

EXAMPLE 183

5-((4-fluorobenzoyl)-N-methyl)amino-3-(1 2,3 6-tetrahydropyridin-4-yl)-1H-indole fumarate

To a solution of 0 59 gm (2 45 mMol) 5-methylamino-3-(1.2.3 6-tetrahydropyridin-4-yl)-1H-indole in 20 mL dimethylformamide were added 0 409 mL (2 9 mMol) triethylamine followed by 0 318 mL (2 7 mMol) 4-fluorobenzoyl chloride After 3 hours the reaction mixture was diluted with 100 mL 2N sodium hydroxide followed by 100 mL ethyl acetate The phases were separated and the aqueous extracted with ethyl acetate The organic extracts were combined and washed sequentially with water and saturated aqueous sodium chloride The remaining organics were dried over sodium sulfate and concentrated under reduced pressure The residue was subjected to flash chromatography, eluting with a gradient of dichloromethane containing 0-5% methanol and 0-0 5% ammonium hydroxide Fractions shown to contain product were combined and concentrated under reduced pressure Fumarate salt was formed in and crystallized from ethyl acetate/ethanol to give 0 868 gm (73 9%) of the title compound as a tan powder

m p =203-206°C (dec)

MS(m/e) 363(M^+)

Calculated for $C_{22}H_{22}N_3OF \cdot C_4H_4O_4$ Theory C 65 13, H 5 47 N, 8 76 Found C, 65 43, H 5 73 N, 8 92

EXAMPLE 184

5-(2-tetrahydrofuranoyl)-3-(1-ethylpiperidin-4-yl)-1H-indole oxalate

To a solution of 0 52 gm (1 55 mMol) 5-(2-furoyl)amino-3-(1-ethyl-1 2,3 6-tetrahydropyridin-4-yl)-1H-indole in 50 mL ethanol and 25 mL tetrahydrofuran were added 0 13 gm 5% palladium on carbon and the mixture hydrogenated at ambient temperature at an initial hydrogen pressure of 60 p s i After 24 hours the reaction mixture was filtered and concentrated under reduced pressure The residue was purified by radial chromatography (2 mm Silica), eluting with 100 5 1 dichloromethane methanol ammonium hydroxide Fractions shown to contain product were combined and concentrated under reduced pressure The residue was dissolved in ethyl acetate and treated with an equivalent of oxalic acid The solid which formed was filtered. washed with ethyl acetate and dried under reduced pressure to give 0 32 gm (47 9%) of the title compound as a white powder

m p =103-105°C

MS(m/e) 341(M^+1)

Calculated for $C_{20}H_{27}N_3O_2 \cdot C_2H_2O_4$ Theory C 61 24, H. 6 77. N 9 74 Found C 61 42 H. 6 80. N. 9 65

EXAMPLE 185

5-methanesulfonylamino-3-(1 2 3,6-pyridin-4-yl)-1H-indole hydrochloride

To a solution of 1 47 gm (26 2 mMol) potassium hydroxide in 10 mL methanol were added 1 0 gm (4 76 mMol) 5-methanesulfonylamino-1H-indole in 5 mL methanol followed by 1 1 gm (7 1 mMol) 4-piperidone hydrochloride monohydrate The resulting suspension was stirred at reflux for 18 hours The reaction mixture was then concentrated under reduced pressure The residual oil was then dissolved in water and the pH of the solution adjusted to 8 0 with 5 0 N hydrochloric acid The solution was saturated with sodium chloride and then extracted with dichloromethane The organic phases were combin d and concentrated under reduced pressure The r sidual solid was crystallized from

methanol/water to give 0 815 gm (52 2%) of the title compound as yellow needles
m p >250°C
MS(m/e) 291(M+)
Calculated for $C_{14}H_{17}N_3SO_2$-HCl Theory C 51 29 H 5 53 N 12 82 Found C 51 53 H 5 55 N 12 73

EXAMPLE 186

5-(4-fluorobenzoyl)amino-3-(1 2 3 6-tetrahydropyridin-4-yl)-1H-indole

To a solution of 5 8 gm (90 mMol) potassium hydroxide in 75 mL methanol were added 9 22 gm (60 mMol) 4-piperidone hydrochloride monohydrate followed by 7 8 gm (30 mMol) 5-(4-fluorobenzoyl)amino-3-(piperidin-4-yl)-1H-indole (Example 182A) This solution was stirred at reflux for 18 hours The reaction mixture was cooled to ambient and then poured slowly into 150 mL water maintaining the temperature of the solution at about 20°C The resulting precipitate was filtered and recrystallized from ethanol to give 4 72 gm (47 2%) of the title compound as tan crystals 0 725 gm of the material were crystallized again from ethanol to provide 0 241 gm light yellow crystals for analysis
m p =241°C (dec)
MS(m/e) 335(M+)
Calculated for $C_{20}H_{18}N_3OF$ Theory C 71 63 H, 5 41 N, 12 53 Found C 71 85. H, 5 50 N, 12 61

EXAMPLE 187

5-(4-fluorobenzoyl)amino-3-(piperidin-4-yl)-1H-indole

Following the procedure described in detail in Example 30 3 93 gm (11 7 mMol) 5-(4-fluorobenzoyl)amino-3-(1 2 3 6-tetrahydropyridin-4-yl)-1H-indole were hydrogenated to give 1 83 gm (49%) of the title compound as colorless crystals m p =229-230°C (methanol)
MS(m/e) 337(M+)
Calculated for $C_{20}H_{20}N_3OF$ Theory C 71 20 H 5 98 N 12 45 Found C 71 46 H, 6 17 N 12 40

General Procedure for the Coupling of Amines with Indole 5-carboxylic acids

A mixture of 15 mg (0 058 mMol) 5-carboxy-3-(1-methyl-1 2 5 6-tetrahydropyridin-4-yl)-1H-indole, 18 mg (0 088 mMol) dicyclohexylcabodiimide 12 mg (0 088 mMol) hydroxybenztriazole, and 1 5 equivalents of an appropriate amine in 2 mL dimethylformamide are heated at 75°C for 18 hours The reaction is allowed to cool and is then loaded onto a VARIAN BOND ELUT SCX™ (Varian Harbor City, CA U S A) ion exchange column (3 mL/0 5 gm) The column is washed with 6 mL methanol and then the desired compound is stripped from the column by eluting with 2M ammonium hydroxide in methanol This eluant is concentrated under reduced pressure and the residue dissolved in 2 mL dichloromethane To this solution is added 0 118 gm (0 118 mMol) of a polystyrene bound isocyanate resin and the mixture agitated for 18 hours The reaction mixture is filtered and concentrated under reduced pressure to provide the amides of the invention If desired the compound may be further purified by loading onto a VARIAN BOND ELUT SAX™ (Varian Harbor City, CA U S A) ion exchange column (10 mL/0 5 gm) The desired compound is stripped from the column by eluting with methanol and concentrating the eluant under reduced pressure The compounds of Examples 188-202 were prepared by this procedure

EXAMPLE 188

N-[(pyridin-2-yl)methyl]-5-carboxamido-3-(1-methyl-1 2 5 6-tetrahydropyridin-4-yl)-1H-indole

Using 2-aminomethylpyridine, 5 2 mg (26%) of the title compound was recovered
MS(m/e) 337(M+1)

EXAMPLE 189

N-[(pyridin-3-yl)methyl]-5-carboxamido-3-(1-methyl-1 2 5 6-tetrahydropyridin-4-yl)-1H-indole

Using 3-aminomethylpyridine 8 3 mg (42%) of the title compound was recovered
MS(m/e) 337(M+1)

EXAMPLE 190

N-[(pyridin-4-yl)methyl]-5-carboxamido-3-(1-methyl-1 2 5 6-tetrahydropyridin-4-yl)-1H-indole

Using 4-aminomethylpyridine 7 9 mg (40%) of the title compound was recovered
MS(m/e) 337(M+1)

EXAMPLE 191

N-[(fur-2-yl)methyl]-5-carboxamido-3-(1-methyl-1 2 5 6-tetrahydropyridin-4-yl)-1H-indole

Using 2-aminomethylfuran, 8 0 mg (51%) of the title compound was recovered
MS(m/e) 335(M^+)

EXAMPLE 192

N-[(tetrahydrofur-2-yl)methyl]-5-carboxamido-3-(1-methyl-1,2 5,6-tetrahydropyridin-4-yl)-1H-indole

Using 2-aminomethyltetrahydrofuran, 3 8 mg (20%) of the title compound was recovered
MS(m/e) 340(M+1)

EXAMPLE 193

5-(pyrrolidin-1-yl)carbonyl-3-(1-methyl-1,2 5 6-tetrahydropyridin-4-yl)-1H-indole

Using pyrrolidine 7 1 mg (39%) of the title compound was recovered
MS(m/e) 309(M^+)

EXAMPLE 194

5-(piperidin-1-yl)carbonyl-3-(1-methyl-1,2,5,6-tetrahydropyridin-4-yl)-1H-indole

Using piperidine 9 7 mg (51%) of the title compound was recovered
MS(m/e) 323(M^+)

EXAMPLE 195

5-(morpholin-1-yl)carbonyl-3-(1-methyl-1 2 5 6-tetrahydropyridin-4-yl)-1H-indole

Using morpholine. 7 2 mg (38%) of the title compound was recovered
MS(m/e) 325(M^+)

EXAMPLE 196

5-(thiomorpholin-1-yl)carbonyl-3-(1-methyl-1 2.5,6-tetrahydropyridin-4-yl)-1H-indole

Using thiomorpholine 11 2 mg (56%) of the title compound was recovered
MS(m/e) 341(M^+)

EXAMPLE 197

5-(4-hydroxypiperidin-1-yl)carbonyl-3-(1-methyl-1 2,5,6-tetrahydropyridin-4-yl)-1H-indole

Using 4-hydroxypiperidine 3 6 mg (18%) of the title compound was recovered
MS(m/e) 340(M+1)

EXAMPLE 198

5-(3-hydroxymethylpiperidin-1-yl)carbonyl-3-(1-methyl-1 2 5 6-tetrahydropyridin-4-yl)-1H-indole

Using 3-hydroxymethylpiperidine 10 1 mg (49%) of the title compound was recovered
MS(m/e) 353(M^+)

EXAMPLE 199

5-(3-(N N-diethylcarboxamido)piperidin-1-yl)carbonyl-3-(1-methyl-1 2 5 6-tetrahydropyridin-4-yl)-1H-indole

Using 3-(N N-diethylcarboxamido)piperidine 11 0 mg (44%) of the title compound was recovered
MS(m/e) 422(M^+)

EXAMPLE 200

5-(4-cyclopentylpiperazin-1-yl)carbonyl-3-(1-methyl-1 2 5,6-tetrahydropyridin-4-yl)-1H-indole

Using 4-cyclopentylpiperazine 8 7 mg (38%) of the title compound was recovered
MS(m/e) 393(M+1)

EXAMPLE 201

5-(4-(2-methoxyethyl)piperazin-1-yl)carbonyl-3-(1-methyl-1 2 5 6-tetrahydropyridin-4-yl)-1H-indole

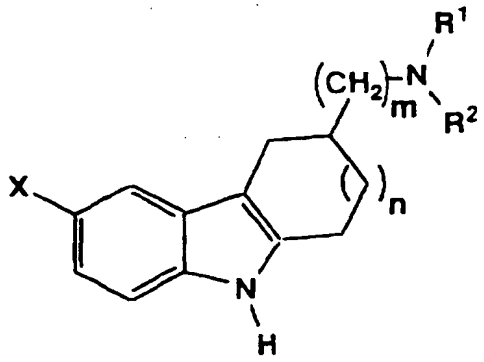
Using 4-(2-methoxyethyl)piperazine. 9 6 mg (43%) of the title compound was recovered
MS(m/e) 383(M+1)

EXAMPLE 202

5-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl-3-(1-methyl-1 2,5,6-tetrahydropyridin-4-yl)-1H-indole

Using 4-(pyridin-2-yl)piperazine. 8 6 mg (36%) of the title compound was recovered
MS(m/e) 402(M+1)

Yet another class of serotonin 5-HT_{1F} receptor agonists are 6-substituted-1 2,3 4-tetrahydro-9H-carbazoles and 7-substituted-10H-cyclohepta[7,6-b]indoles of Formula V



V

wherein

R^1 and R^2 are independently hydrogen C_1-C_4 alkyl. or CH_2CH_2-Aryl where Aryl is phenyl. phenyl monosubstituted with halo. or 1-(C_1-C_6 alkyl)pyrazol-4-yl
X is -OH -NHC(O)R^3. -NHC(Y)NHR^4 -NHC(O)OR^5 -C(O)R^6 or -$NHSO_2R^7$

R^3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_5-C_8 cycloalkyl, phenyl, substituted phenyl, naphthyl, (C_1-C_4 alkylene)phenyl, thienylmethyl, or a heterocycle,
R^4 is C_1-C_6 alkyl, phenyl, or phenyl disubstituted with halo,
R^5 is C_1-C_6 alkyl, C_2-C_6 alkenyl, benzyl or phenyl monosubstituted with halo,
R^6 is C_1-C_6 alkyl, phenyl, or phenyl monosubstituted with halo or C_1-C_4 alkoxy,
R^7 is dimethylamino, phenyl or phenyl monosubstituted with halo or C_1-C_4 alkyl,
m is 0 or 1,
n is 1 or 2, and
Y is S or O, and pharmaceutically acceptable salts and hydrates thereof.

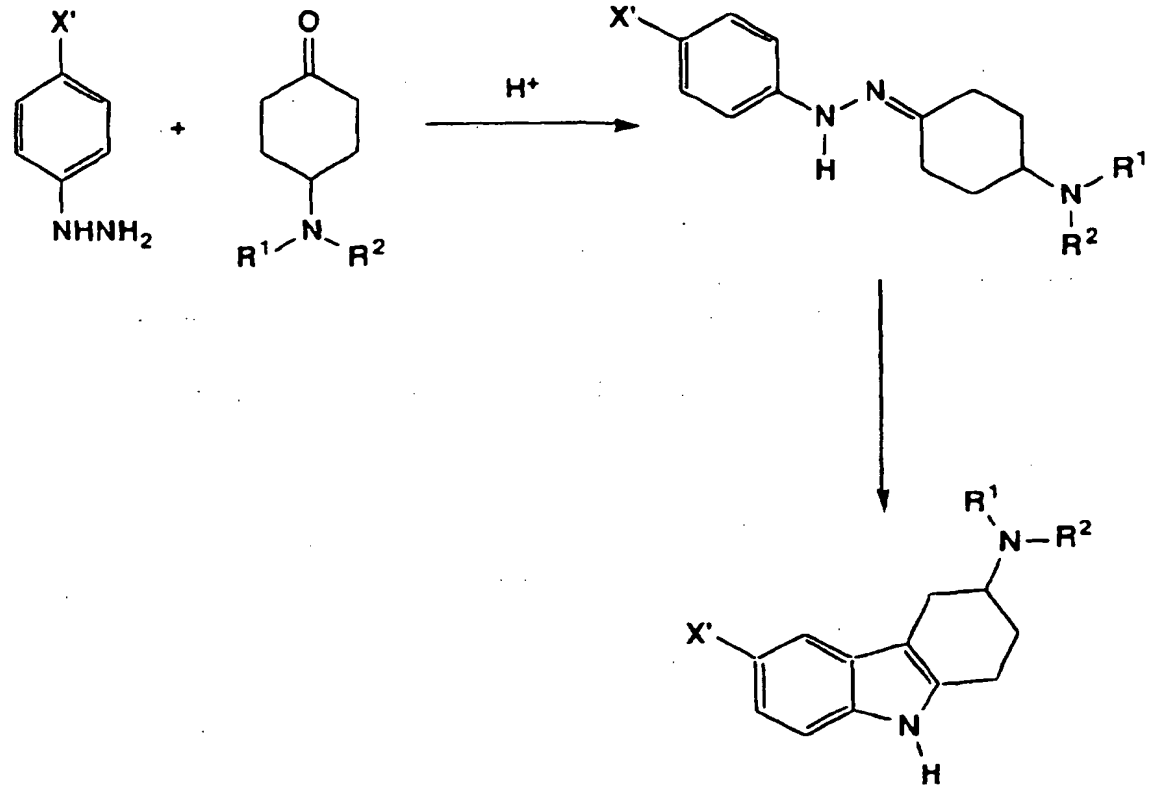
The general chemical terms used in the formulae above have their usual meanings. For example, the terms "alkyl, alkoxy and alkylthio" include such groups as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 2-pentyl-, 3-pentyl-, neopentyl, hexyl, heptyl, and the like. The term "alkenyl" includes allyl, 1-buten-4-yl, 2-methyl-1-buten-4-yl, 2-buten-4-yl, 1-penten-5-yl, 4-methyl-2-penten-5-yl, 2-penten-5-yl, 3-penten-5-yl, 1-hexen-6-yl, 2-hexen-6-yl, 3-hexen-6-yl, 4-hexen-6-yl and the like. The term "acyl" includes formyl, acetyl, propanoyl, butanoyl, and 2-methylpropanoyl. The term "cycloalkyl" includes such groups as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The term "(C_1-C_4 alkylene)phenyl" includes such groups as benzyl, phenethyl, 1-phenyl-2-methylpropyl, phenpropyl, and phenbutyl. The term "(C_1-C_4 alkyl)sulfonyl" includes methanesulfonyl, ethanesulfonyl, propanesulfonyl, isopropanesulfonyl, butanesulfonyl, and the like. The term "halo" includes fluoro, chloro, bromo, and iodo.

The term "substituted phenyl" is taken to mean a phenyl group substituted with one substituent selected from the group consisting of halo, C_1-C_4 alkyl, C_1-C_8 alkoxy, C_1-C_4 alkylthio, nitro, cyano, di(C_1-C_4 alkyl)amino, trifluoromethyl, trifluoromethoxy, phenyl, C_1-C_4 acyl, benzoyl or (C_1-C_4 alkyl)sulfonyl or two to three substituents independently selected from the group consisting of halo, nitro, C_1-C_4 alkyl, or C_1-C_4 alkoxy.

The term "heterocycle" is taken to mean furyl, thienyl, pyridinyl, pyrrolyl, N-methylpyrrolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolinyl, benzofuranyl, thionaphthyl, or indolyl all optionally substituted with halo, C_1-C_4 alkyl or C_1-C_4 alkoxy.

The compounds of Formula V are prepared by methods well known to one of ordinary skill in the art. Compounds where m is 0 and n is 1 are members of the class commonly known as 6-substituted-3-amino-1,2,3,4-tetrahydro-9H-carbazoles. Members of this class are conveniently prepared by the Fischer indole synthesis as illustrated in Synthetic Scheme B-I. X' is bromo, benzyloxy, $R^3C(O)NH$-, $R^4NHC(Y)NH$-, $R^5OC(O)NH$-, or R^7SO_2NH-. R^1 and R^2 are independently C_1-C_6 alkyl, benzyl or, together with the nitrogen, form a phthalimido group and Y, R^3, R^4, R^5 and R^7 are as previously defined.

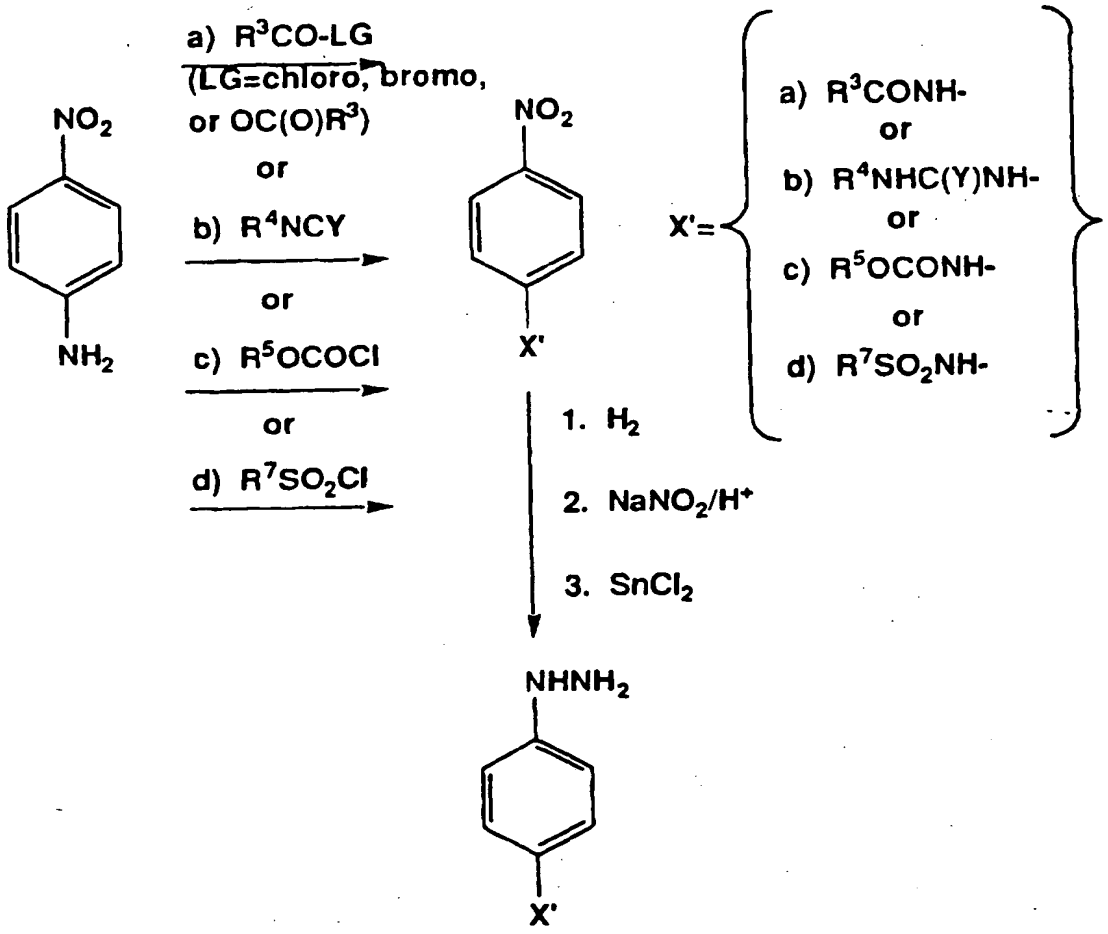
Synthetic Scheme B-I



The phenylhydrazine and 4-aminocyclohexanone are condensed together in a suitable solvent typically a lower alkanol such as ethanol in the presence of a catalytic amount of acid, such as hydrogen chloride to give the resultant phenylhydrazone The reaction is typically performed at from about room temperature to reflux for from about 1 to 24 hours Once the condensation is complete the resulting phenylhydrazone may be isolated from the reaction mixture by the addition of water or an aqueous solution of a base such as potassium carbonate if desired The product separates from the mixture as an oil or a solid The product may be extracted with a water immiscible solvent typically dichloromethane or filtered if appropriate The product may be used in the next step with or without further purification The phenylhydrazone undergoes a Fischer indole cyclization in the presence of excess acid This may be accomplished by dissolving the phenylhydrazone in a neat acid for example acetic acid Alternatively the phenyl hydrazone may be dissolved in a lower alkanol which has been treated with an acid for example ethanolic hydrogen chloride If the phenylhydrazone prepared as described above requires no further purification, the original reaction mixture may conveniently be treated with an appropriate acid without isolation of the phenylhydrazone Many times the Fischer indole cyclization occurs upon formation of the phenylhydrazone giving the desired product in one step The reaction is performed at from about room temperature to reflux for from about 1 to 24 hours The reaction product may be recovered by direct filtration or by extraction after removal of solvent and neutralization of acid by the addition of aqueous base The product may be purified by recrystallization or chromatography as required

The phenylhydrazines required for the preparation of compounds of Formula V are either commercially available or may be prepared by methods well known to those skilled in the art Phenylhydrazines where X' is $R^3C(O)NH$-$R^4NHC(Y)NH$-, $R^5OC(O)NH$- and R^7SO_2NH- are prepared from 4-nitroaniline as described in Synthetic Scheme B-II Y, R^3 R^4 R^5 and R^7 are as previously defined

Synthetic Scheme B-II



Compounds where X' is $R^4NHC(Y)NH$- are prepared by treating a solution of 4-nitroaniline in a suitable solvent such as chloroform or dichloromethane with an appropriate isocyanate or isothiocyanate If necessary, an excess of the isocyanate or isothiocyanate is employed to ensure complete reaction of the starting amine The reactions are performed at about ambient to about 45°C for from about three hours to about three days Typically, the product may be isolated by washing the reaction with water and concentrating the remaining organics under reduced pressure When an excess of isocyanate or isothiocyanate has been used however, a polymer bound primary or secondary amine, such as an aminomethylated polystyrene may be conveniently added to react with the excess reagent Isolation of products from reactions where a polymer bound reagent has been used is greatly simplified, requiring only filtration of the reaction mixture and then concentration of the filtrate under reduced pressure The product from these reactions may be purified chromatographically or recrystallized from a suitable solvent if desired

Substituted nitroanilines where X' is $R^5OC(O)NH$- are prepared by treating a solution of 4-nitroaniline in a suitable solvent such as chloroform or dichloromethane, with an appropriate chloroformate in the presence of a base, or by treatment with an appropriate carbonate of structure $(R^5O)_2C(O)$ Suitable bases include amines typically used as acid scavengers such as pyridine or triethylamine, or commercially available polymer bound bases such as polyvinylpyridine Likewise substituted nitroanilines where X' is $R^3C(O)NH$- or R^7SO_2NH- are prepared by reacting 4-nitroaniline with an appropriate carboxylic acid or sulfonyl chloride, bromide or anhydride optionally in the presence of an acylation catalyst such as dimethylaminopyridine, in the presence of a suitable base such as those described *supra*

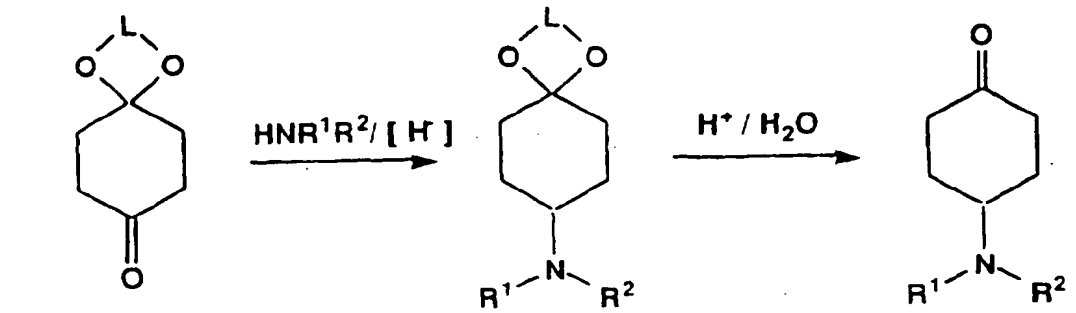
Alternatively, substituted nitroanilines where X' is $R^3C(O)NH$- are prepared by reacting 4-nitroaniline with an appropriate carboxylic acid in the presence of typical peptide coupling reagents such as N,N'-carbonyldiimidazole (CDI), N N'-dicyclohexylcarbodiimide (DCC) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) A polymer supported form of EDC has been described (*Tetrahedron Letters*, 34(48) 7685 (1993)) and is very useful for the

preparation of the compounds of the present invention The product from these reactions is isolated and purified as described above

The substituted nitroanilines are hydrogenated over a precious metal catalyst preferably platinum on carbon and hydrogenated at about ambient temperature at an initial pressure of about 60 p s i for from about 1 to 24 hours in a suitable solvent such as a lower alkanol or tetrahydrofuran to give the corresponding amino derivative This amino derivative is then dissolved in a concentrated acid such as phosphoric hydrochloric or hydrobromic acid and treated with sodium nitrite at a temperature about or below 0°C After stirring for about an hour the reaction mixture is added to a solution of tin(II) chloride in concentrated hydrochloric acid and the mixture stirred at about 0°C for about an hour The product is isolated by treating the reaction mixture with an aqueous base until it is strongly basic and then extracting with a water immiscible solvent such as ethyl acetate The hydrazine product may be further purified by chromatography or crystallization prior to further reaction if desired

The 4-substituted cyclohexanones required for the preparation of compounds of Formula V are available by methods well known in the art as illustrated in Synthetic Scheme B-III R^1 and R^2 independently hydrogen C_1-C_6 alkyl or benzyl

Synthetic Scheme B-III

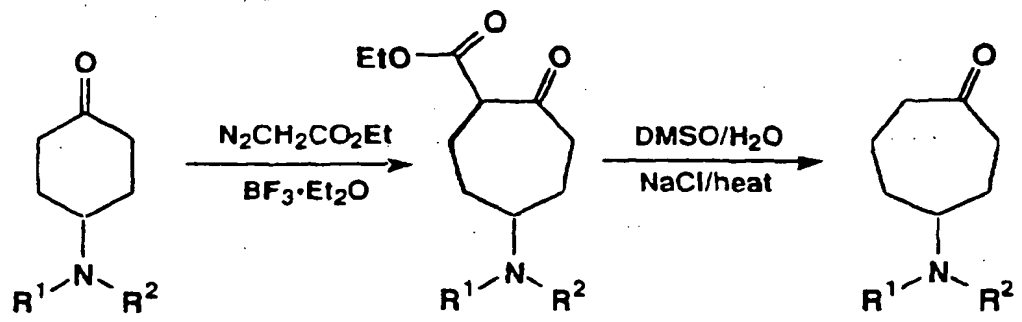


The 1 4-cyclohexanedione monoketal is reductively aminated with an appropriate amine under standard conditions to give the corresponding 4-aminocyclohexanone ketal The ketal is then deprotected under aqueous acid conditions to prepare the corresponding 4-aminocyclohexanone

Compounds of Formula V where R^1=R^2=H are prepared from 4-(l-phthlimidyl)cyclohexanone which is available by methods well known in the art for example, King *et al* *(Journal of Medicinal Chemistry,* **36**, 1918 (1993)) Briefly, 4-aminocyclohexanol is reacted first with N-carbethoxyphthalimide and the resulting 4-(1-phthalimidyl)cyclohexanol treated with pyridinium chlorochromate to give the desired ketone The resultant 4-(1-phthlimidyl)cyclohexanone is then reacted with an appropriate phenylhydrazine followed by Fischer indole cyclization to prepare the corresponding 3-(1-phthalimidyl)carbazole The phthalimide is then removed by reaction with hydrazine at a convenient point after the Fischer indole synthesis to provide compounds where R^1=R^2=H

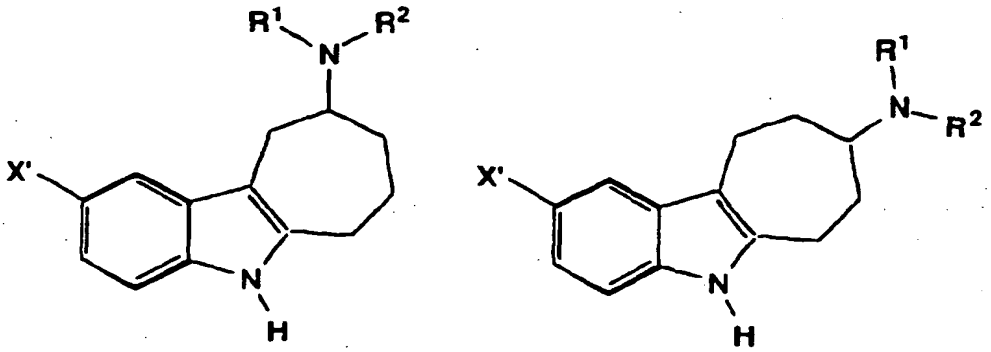
Compounds of Formula V where m=0 and n=1 are 7-substituted-4-amino-10H-cyclohepta[6 7-b]indoles These compounds are prepared substantially as described for the 6-substituted-3-amino-1 2 3 4-tetrahydro-9H-carbazoles as illustrated in Synthetic Scheme B-I except that a 4-aminocycloheptanone replaces the 4-aminocyclohexanone in the synthesis The 4-aminocycloheptanones required for the synthesis of compounds of Formula V may be prepared as described in Synthetic Scheme B-IV R^1 and R^2 are independently C_1-C_6 alkyl or benzyl or together with the nitrogen form the phthalimide moiety

Synthetic Scheme B-IV



The appropriate 4-aminocyclohexanone in an appropriate solvent, for example diethyl ether is treated with an appropriate Lewis acid such as boron trifluoride for about 20 minutes to about an hour at room temperature To this solution is then added ethyl diazoacetate and the resulting mixture is stirred for about 1 hour to about 24 hours at room temperature The resulting 2-ethoxycarbonyl-5-aminocycloheptanone is isolated by diluting the reaction mixture with aqueous sodium carbonate and extracting with a water immiscible solvent such as diethyl ether The reaction product is then directly dissolved in dimethylsulfoxide which contains sodium chloride and water The reaction mixture is heated to about 170° for from about 1 to about 24 hours to effect the decarboxylation The desired 4-aminocycloheptanone is recovered by diluting the reaction mixture with water and extracting with an appropriate solvent such as diethyl ether The reaction product may be purified by column chromatography, if desired, prior to further reaction

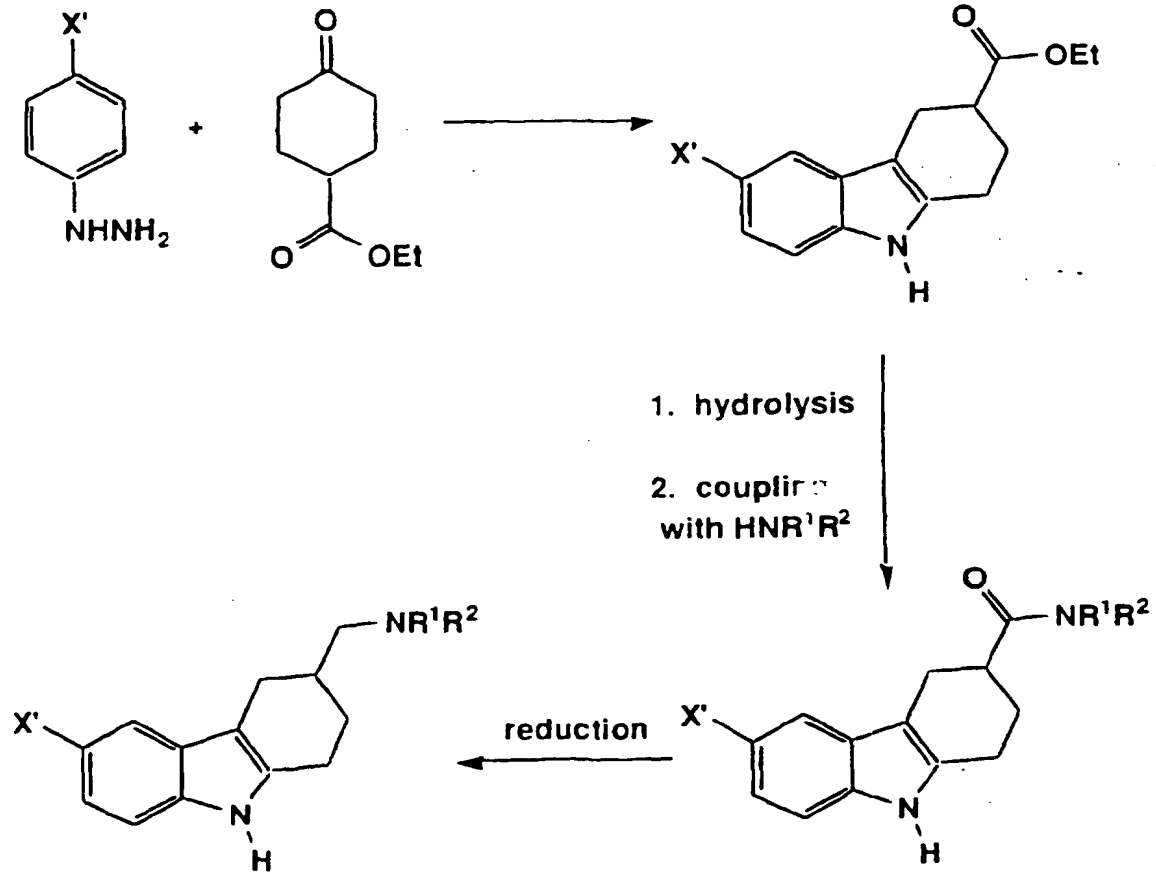
After reaction with an appropriate phenylhydrazine, the corresponding 4-aminocycloheptanonephenylhydrazone is subjected to the same Fischer indole cyclization conditions as described above The asymmetry in the cycloheptanone, however leads to the production of the following two isomers



Isomers A and B may be separated by crystallization or chromatography at any convenient point in the synthesis of the compounds of the invention

Compounds of Formula V where m=1 and n=1 are conveniently prepared by the procedure described in Synthetic Scheme B-V R^1 and R^2 are independently C_1-C_6 alkyl or benzyl and X' is benzyloxy or bromo

Synthetic Scheme B-V

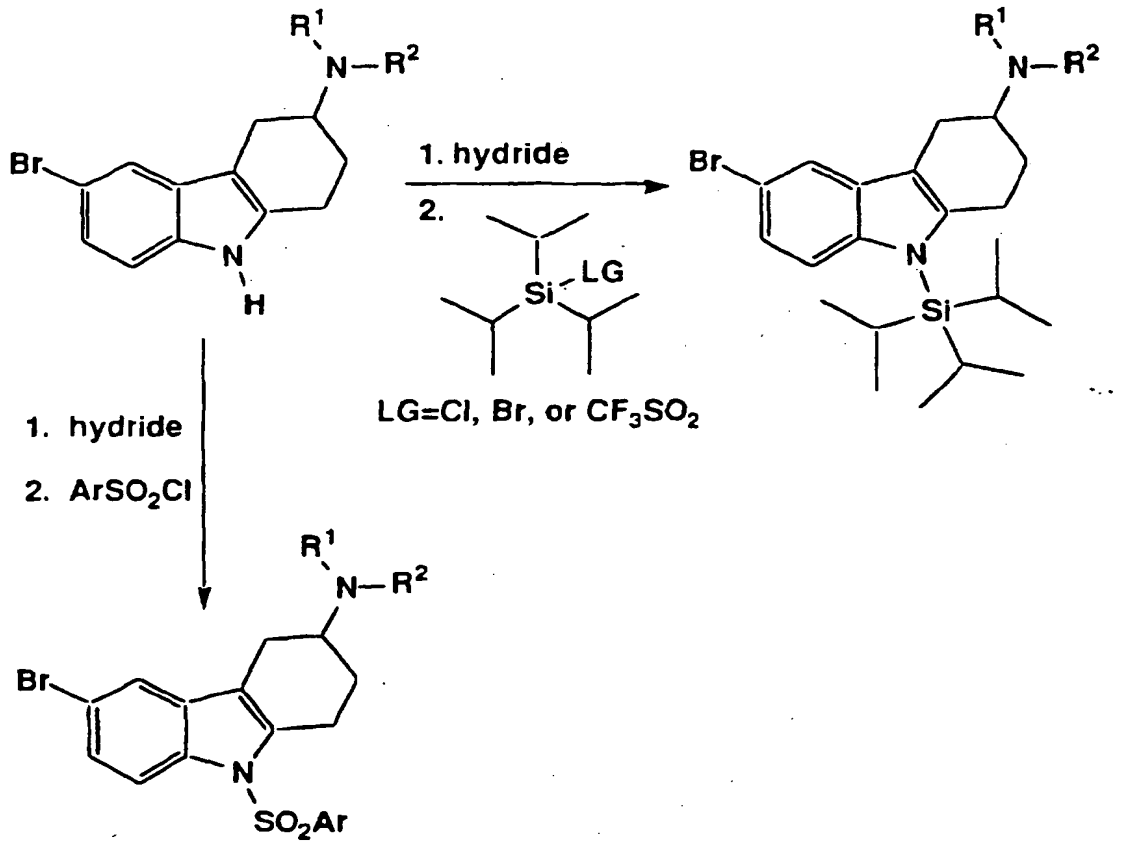


The appropriate phenylhydrazine and ethyl cyclohexanone-4-carboxylate are condensed together to prepare the corresponding phenylhydrazone which is then subjected to Fischer indolization conditions as described previously The resultant ethyl 3-carboxy-6-substituted-9H-1 2 3 4-tetrahydrocarbazole is subjected to basic ester hydrolysis conditions and the carboxylate subsequently protonated to give the corresponding carboxylic acid The carboxylic acid is coupled to an amine of structure HNR^1R^2 under any of the amide forming conditions described earlier The resulting amide is reduced with an appropriate hydride reducing agent such as lithium aluminum hydride or diborane under standard conditions to give the corresponding N-substituted-3-methylamino-6-substituted-9H-1 2 3 4-tetrahydrocarbazole This product may be used as is or may be purified by chromatography or crystallization as desired prior to further reaction

The skilled artisan will appreciate that ethyl 4-carboxycyclohexanone may undergo the ring expansion described above to give the corresponding ethyl 4-carboxycycloheptanone This substrate may then be subjected to the same sequence of steps described in Synthetic Scheme B-V to give the corresponding 3 and 4-aminomethylcyclohep-ta [7,6-b]indoles The isomers may be separated at any convenient point in the synthesis after the Fischer indolization step

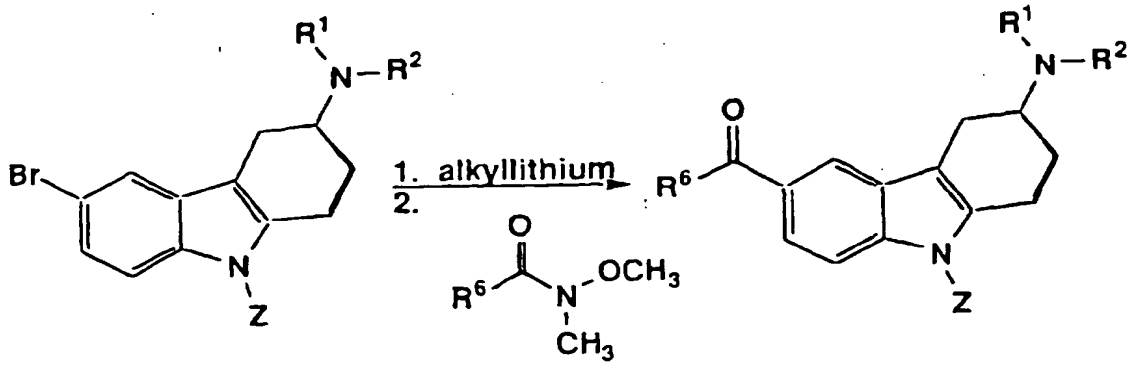
Compounds of Formula V where X is bromo are useful intermediates for the introduction of a variety of substituents into the 6- or 7-position of the corresponding tetrahydrocarbazole or cyclohepta[7 6-b]indole nuclei respectively Prior to manipulation of the bromo substituent however, the indole nitrogen must first be protected as illustrated in Synthetic Scheme B-VI R^1 and R^2 are C_1-C_6 alkyl or benzyl and Ar is phenyl or 2 4 6-triisopropylphenyl

Synthetic Scheme B-VI



A solution of the starting material in an a suitable solvent such as tetrahydrofuran or diethyl ether, are added to a suspension of an alkali metal hydride preferably potassium hydride, in the same solvent The deprotonation is performed at from about -10°C to about ambient temperature for about an hour To this solution is then added an appropriate arylsulfonyl chloride, triisopropylsilyl halide, or triisopropylsilyl triflate and the reaction is allowed to proceed for from about 1 to 24 hours The indole nitrogen protected derivative is isolated by treating the reaction mixture with ice to decompose any unreacted hydride, diluting the reaction mixture with water. and then extracting the product with a water immiscible solvent such as dichloromethane diethyl ether or ethyl acetate The isolated product may be used as recovered for further reactions or purified by crystallization or chromatography as desired The bromo substituted substrate so protected may be used to provide compounds of Formula V where X is $R^6C(O)$- as described in Synthetic Scheme B-VII R^1 and R^2 are C_1-C_6 alkyl or benzyl and Z is phenylsulfonyl. 2.4,6-triisopropylphenylsulfonyl or triisopropylsilyl and R^6 is as previously defined

Synthetic Scheme B-VII

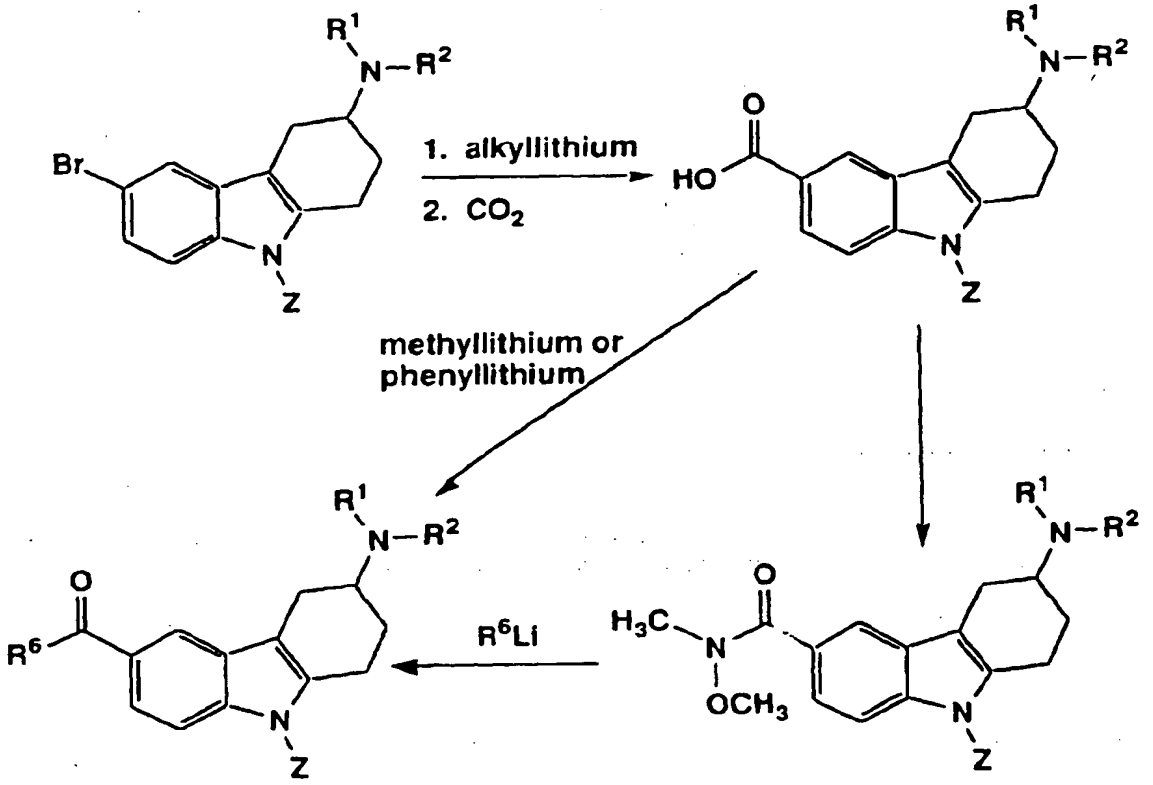


A solution of the bromo compound in an appropriate solvent, such as tetrahydrofuran or diethyl ether, is treated with an alkyllithium such as n-butyl- or t-butyllithium, at a temperature of about -70°C for about an hour to effect a hologen-metal exchange The resultant anion solution is added to a solution of the appropriate N-methyl-N-methoxyamide in an appropriate solvent such as tetrahydrofuran or diethyl ether at a temperature of about -70°C The reaction mixture is then allowed to warm gradually to room temperature over from about 1 hour to about 24 hours The resulting product is isolated by diluting the reaction mixture with water or aqueous ammonium chloride and extracting with a water immiscible solvent such as dichloromethane The product may be further purified by chromatography or recrystallization as necessary.

The N-methyl-N-methoxyamides are conveniently prepared by reacting a carboxylic acid of formula R^6-CO_2H with oxalyl chloride or thionyl chloride under standard conditions to prepare the corresponding acid chloride This acid chloride is then treated with N-methoxymethylamine to prepare the required amide

Alternatively, the compounds where X is $R^6C(O)$- may be prepared by the procedure illustrated in Synthetic Scheme B-VIII R^1 and R^2 are C_1-C_6 alkyl or benzyl and Z is phenylsulfonyl 2 4,6-triisopropylphenylsulfonyl or triisopropylsilyl and R^6 is as previously defined

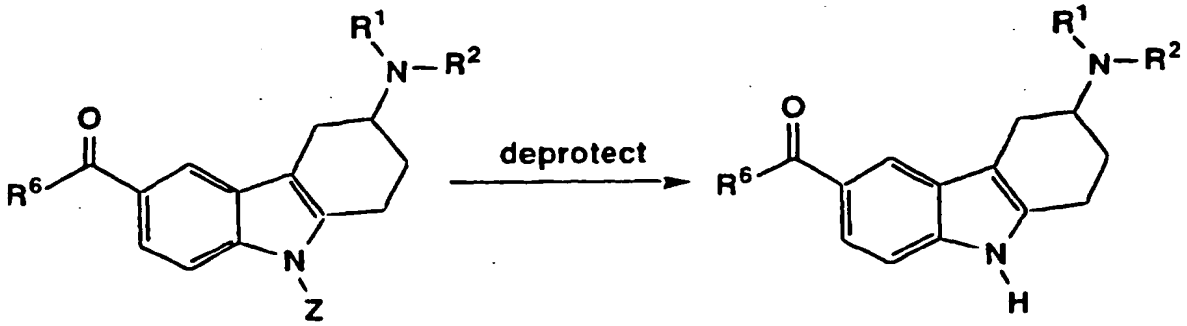
Synthetic Scheme B-VIII



The anion solution is prepared as previously described and is then saturated with carbon dioxide to prepare the corresponding carboxylic acid This is acid may then be treated directed with an alkyllithium. such as methyllithium, to prepare compounds where R^6 is C_1-C_4 alkyl. Alternatively, the carboxylic acid may be converted to its corresponding N-methyl-N-methoxyamide using the procedures previously described This amide is then treated with a compound of formula R^6Li to give the desired compound Compounds of formula R^6Li are commercially available or may be prepared by halogen-metal exchange from an R^6-halide under the conditions previously described

The final step in the sequence requires deprotection of the indolic nitrogen to give the compounds of the invention as illustrated in Synthetic Scheme B-IX R^1 and R^2 are independently hydrogen, C_1-C_6 alkyl or benzyl, Z is phenylsulfonyl. 2 4.6-triisopropylphenylsulfonyl or triisopropylsilyl. and R^6 is as previously defined

Synthetic Scheme B-IX

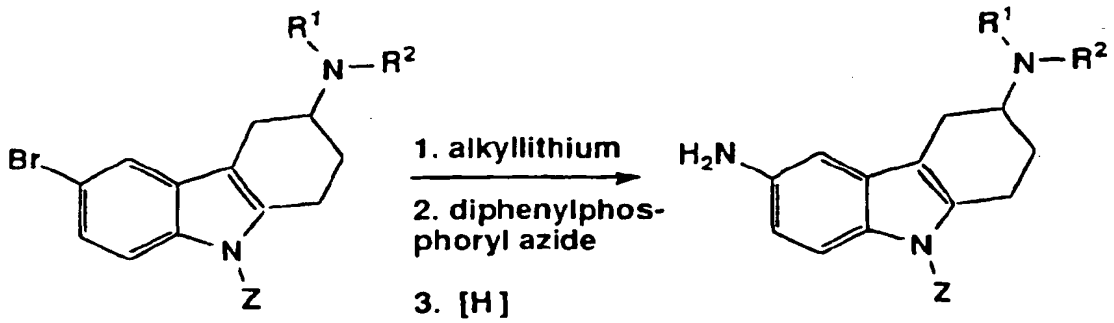


When Z is arylsulfonyl the protecting group may be removed by basic hydrolysis in a lower alkanol such as methanol or ethanol When Z is triisopropylsilyl deprotection is conveniently effected by treatment with a fluoride anion reagent preferably tetrabutylammonium fluoride under standard conditions

Compounds of Formula V where X is $R^6C(O)$- and R^1 and R^2 are independently hydrogen are available by subjecting the corresponding 3-benzylamino compounds to catalytic hydrogenation conditions over a precious metal catalyst such as palladium or platinum on carbon or over Raney nickel These reactions are typically performed in a lower alkanol or tetrahydrofuran at room temperature to about 60°C for from about 1 hour to 24 hours at a hydrogen pressure of about 60 p s i This hydrogenolysis may be performed before or after the deprotection of the indole nitrogen as desired Additionally compounds of Formula V where X is -OH are prepared by hydrogenolysis of the corresponding benzyl ether under the same conditions as described above

The protected bromo compounds described in Synthetic Scheme B-VI are also useful for the preparation of the corresponding amine derivatives as described in Synthetic Scheme B-X R^1 and R^2 are independently C_1-C_6 alkyl or benzyl, and Z is phenylsulfonyl 2 4 6-triisopropylphenylsulfonyl or triisopropylsilyl

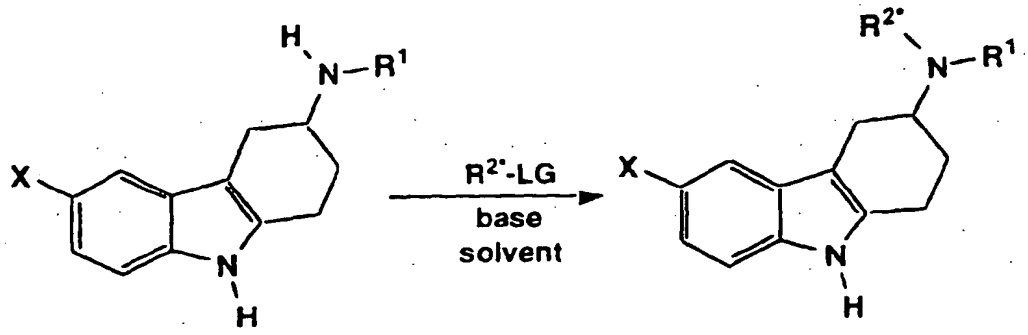
Synthetic Scheme B-X



The anion is prepared according to the procedure previously described The anion solution is then added to a solution of diphenylphosporyl azide in an appropriate solvent such as such as tetrahydrofuran or diethyl ether at a temperature of about -70°C The reaction mixture is maintained at this temperature for about two hours and is then treated with an appropriate hydride reducing agent such as sodium bis(2-methoxyethoxy)aluminum hydride in toluene The resulting reaction mixture is allowed to warm to room temperature over about an hour The amine product is isolated by first treating the reaction mixture with ice to destroy any excess hydride reagent, filtering any solid which has formed, diluting the filtrate with water and extracting the product into a water immiscible solvent such as dichloromethane The amine product prepared by this procedure is useful for preparation of compounds where X is $R^3C(O)NH$- $R^4NHC(Y)NH$-, $R^5OC(O)NH$-, or R^7SO_2NH- by the reaction conditions described previously for the functionalization of nitroanilines in Synthetic Scheme II Alternatively compounds where X is $R^3C(O)NH$- or $R^5OC(O)NH$- may be subjected to acidic or basic hydrolysis conditions to prepare the corresponding amine which may then be converted to other compounds of Formula V

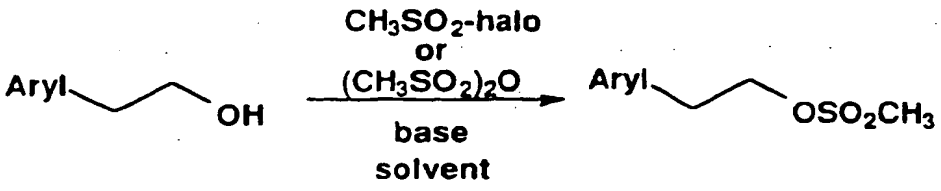
Compounds where either or both of R^1 or R^2 are hydrogen may be further functionalized to prepare other compounds of Formula V by reductive alkylation Under these conditions the primary or secondary amine is reacted with an appropriate aldehyde or ketone to prepare the corresponding imine or enamine The imine or enamine is then reduced to the desired compound by catalytic hydrogenation or by reduction with an appropriate hydride reducing reagent in the presence of an acid Preferably the transformation is performed by direct alkylation as illustrated in Synthetic Scheme B-XI R^1 is hydrogen or C_1-C_6 alkyl $R^{2'}$ is C_1-C_6 alkyl or arylethyl, and X and arylethyl are as previously defined

Synthetic Scheme B-XI



The starting amine and a base are combined in the reaction solvent followed by the addition of the alkylating agent The reaction solvent may be any non-reactive solvent typically used for alkylations of this type such as acetonitrile dimethylformamide or N-methyl-2-pyrrolidinone limited by the solubility of the substrates The base must be sufficiently basic to neutralize the acid generated during the progress of the reaction but not so basic as to deprotonate other sites in the substrate giving rise to other products Additionally the base must not compete to any great extent with the substrate for the alkylating agent Bases typically used for these reactions are sodium carbonate or potassium carbonate The reaction mixture is typically stirred at room temperature to 80°C for about 8 hours to 3 days The alkylated products are isolated by concentration of the reaction mixture under reduced pressure followed by partitioning of the resultant residue between water and a suitable organic solvent such as ethyl acetate diethyl ether, dichloromethane, ethylene chloride chloroform or carbon tetrachloride The isolated product may be purified by chromatography, crystallization from a suitable solvent salt formation or a combination of these techniques

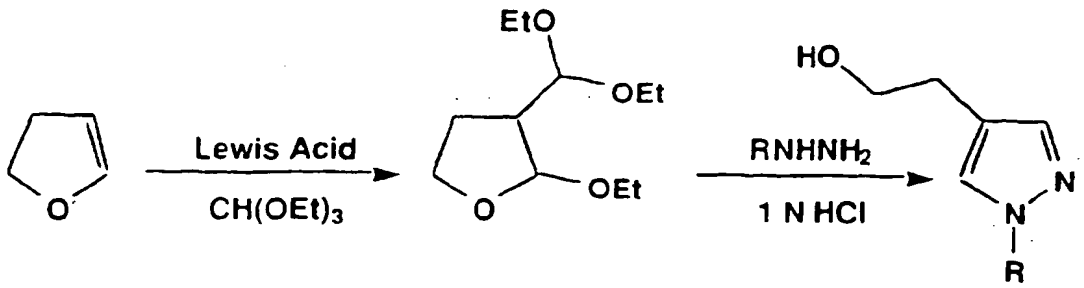
The leaving group (LG) of the alkylating agents may be chloro, bromo iodo, methanesulfonyloxy, trifluoromethanesulfonyloxy, 2,2,2-trifluoroethanesulfonyloxy, benzenesulfonyloxy, p-bromobenzenesulfonyloxy p-nitrobenzenesulfonyloxy or p-toluenesulfonyloxy. all of which are useful for the preparation of compounds of Formula V The specific alkylating agent employed is determined by its commercial availability or a convenient synthesis from commercially available starting materials The preferred alkylating agents for synthesis of compounds of Formula V are selected from those where the leaving group is chloro, bromo, iodo or methanesulfonyloxy Alkylating agents where the leaving group is chloro are prepared from the corresponding alcohol by standard methods preferably by treating the alcohol with neat thionyl chloride at ambient temperature Alkylating agents where the leaving group is methanesulfonyloxy are prepared from the corresponding alcohols as described below



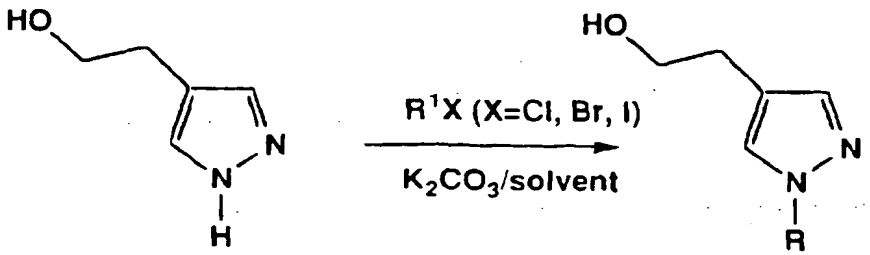
The alcohol is dissolved in a suitable anhydrous solvent such as tetrahydrofuran diethyl ether, p-dioxane or acetonitrile which contains the base The base must be sufficiently basic to neutralize the acid generated during the progress of the reaction but not so basic as to deprotonate other sites in the substrate giving rise to other products Additionally the base must not compete to any great extent with the substrate for the sulfonating reagent and must have sufficient solubility in the reaction solvent Bases typically used in these reactions are tertiary amines such as pyridine. triethylamine or N-methylmorpholine To the reaction mixture is then added the sulfonating reagent with cooling The sulfonating reagent may be a methanesulfonyl halide such as the chloride or methanesulfonic anhydride The reaction mixture is allowed to react from 1 hour to 24 hours at ambient temperature The product is isolated by concentrating the reaction mixture under reduced pressure followed by partitioning the residue between water and an appropriate organic solvent such as dichloromethane. ethylene chloride. chloroform or carbon tetrachloride The isolated product is used directly in the alkylation step

The starting alcohols required for the synthesis of compounds of Formula V are either commercially available or

may be prepared by employing well established synthetic methodology A general scheme for the synthesis of a number of the required alcohols is described below



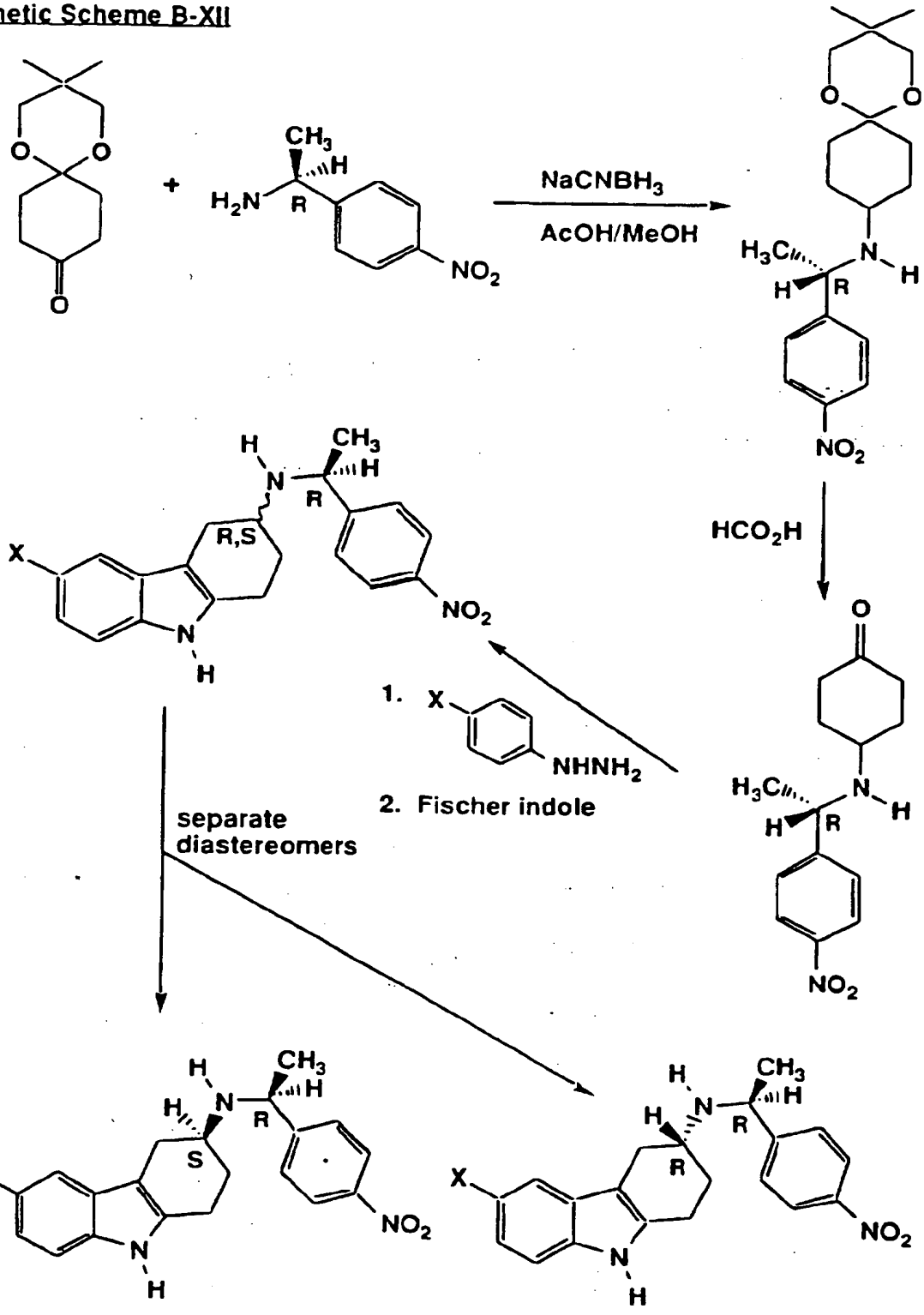
4 5-Dihydrofuran or 3 4-dihydro-2H-pyran is treated with triethylorthoformate in the presence of a Lewis acid preferably boron trifluoride diethyl etherate for from 1 to 4 days at ambient temperature After treating the reaction mixture with an anhydrous base such as potassium carbonate the intermediate diacetal is distilled from the reaction mixture This diacetal is now treated with an appropriate hydrazine typically commercially available or synthesized by standard techniques in aqueous acid at reflux for 4-24 hours The product is recovered by treatment of the reaction mixture with base and extraction of the base into methylene chloride The alcohol so recovered is suitable for use without further purification When R is hydrogen the alcohol can be further modified by direct alkylation of one of the pyrazole nitrogens as described below



The alkylation is performed in a suitable solvent typically dimethylformamide acetonitrile or acetone with potassium carbonate and the desired alkylating agent The alkylating agent is a lower alkyl halide preferably the bromide or iodide The reaction is performed at ambient to reflux temperature for 1 hour to 3 days

The compounds of Formula V possess a chiral center and as such exist as racemic mixtures or individual enantiomers Racemates and the individual enantiomers are all useful for the method of the present invention The individual enantiomers may be resolved by fractional crystallization of salts of the racemic bases and enantiomerically pure acids for example. ditolyltartaric acid Alternatively the individual enantiomers may be prepared by the use of a chiral auxiliary during the preparation of the compound as described in the following Synthetic Scheme B-XII X is bromo benzyloxy nitro $R^3C(O)NH$- $R^4NHC(Y)NH$- $R^5OC(O)NH$- or R^7SO_2NH- and Y R^3 R^4 R^5 and R^7 are as previously defined

Synthetic Scheme B-XII



1 4-cyclohexanedione mono-(2 2-dimethylpropane-1 3-diol)ketal is reductively aminated under standard conditions with an enantiomer of α-methyl-(4-nitrophenyl)ethylamine (Synthetic Scheme B-XII illustrates the use of the R-

(+)-enantiomer) The ketal is removed as described previously and the resulting aminocyclohexanone is subjected to the reaction conditions described for Synthetic Scheme I to give a diastereomeric mixture The diastereomers are then separated by chromatography or fractional crystallization The amine may then be treated if desired with an appropriate alkylating agent for example an appropriate alkyl halide to prepare the corresponding quaternary salt prior to cleavage of the a-methyl-(4-nitrophenyl)ethyl moiety

Cleavage of the a-methyl-(4-nitrophenyl)ethyl moiety is achieved by reduction of the 4-nitro group followed by acid catalyzed solvolysis of the resulting α-methyl-(4-aminophenyl)ethyl moiety Reduction of the nitro group can be accomplished by a wide range of reducing agents including for example titanium tetrachloride lithium aluminum hydride or zinc/acetic acid or by catalytic hydrogenation Solvolytic cleavage takes place when the monohydrochloride (or other monobasic salt) of the reduction product is treated with water or an alcohol at room temperature or in some instances, at elevated temperatures A particularly convenient condition for removing the α-methyl-(4-nitrophenyl)ethyl moiety is hydrogenation of the amine monohydrochloride in methanol over a platinum catalyst

The reactions as illustrated in Synthetic Schemes B-VI through B-XII are for the compounds of Formula V which are carbazoles The skilled artisan, however will appreciate that the chemistry illustrated is applicable to the other classes of compounds of Formula V as well The skilled artisan will also appreciate that the order in which the steps are performed to prepare the compounds of Formula V are not important in many cases

Preparation B-I

6-bromo-3-dimethylamino-9-triisopropylsilyl-1 2 3 4-tetrahydro-9H-carbazole

4-dimethylaminocyclohexanone 2 2-dimethylpropane-1 3-diol)ketal

To a solution of 25 0 gm (554 6 mMol) dimethylamine in 500 mL methanol were added 50 0 gm (252 2 mMol) 1 4-cyclohexanedione mono-2 2-dimethylpropane-1 3-diol ketal and the reaction mixture was allowed to stir for 2 hours at room temperature To this solution were then gradually added 31 69 gm (504 3 mMol) sodium cyanoborohydride Once this addition was complete acetic acid was added to adjust the mixture to a pH of about 6 The pH was monitored periodically and acetic acid additions continued to maintain the pH at about 6 When the addition of acetic acid no longer resulted in gas evolution, the reaction mixture was allowed to stir at room temperature for 18 hours The reaction mixture was then concentrated under reduced pressure to a volume of about 100 mL and was then partitioned between 1N sodium hydroxide and dichloromethane The remaining aqueous phase was treated with saturated aqueous sodium chloride and was again extracted with dichloromethane These organic phases were combined dried over sodium sulfate and concentrated under reduced pressure to give 40 15 gm (70%) of the desired compound as a yellow oil
MS(m/e) 228(M+1)

4-dimethylaminocyclohexanone

A solution of 18 4 gm (81 mMol) 4-dimethylaminocyclohexanone (2 2-dimethylpropane-1 3-diol)ketal in 250 mL 90% formic acid were heated at reflux for 3 hours The reaction mixture was then stirred at room temperature for 3 days The reaction mixture was then diluted with 250 mL water and was concentrated to a volume of about 250 mL on a rotary evaporator The dilution/concentration sequence was then repeated two more times The residue was then further concentrated to a volume of about 50 mL, made basic with 5 N sodium hydroxide and extracted with dichloromethane The organic phases were combined dried over sodium sulfate and concentrated under reduced pressure to give 11 8 gm (100%) of the desired compound as a yellow oil
MS(m/e) 141 (M^+)
NMR($CDCl_3$) δ2 50 (m 2H) 2 28 (m 2H) 2 28 (m, 6H) 2 01 (m, 2H) 1 80 (m 2H)

4-dimethylaminocyclohexanone 4-bromophenylhydrazone

To a mixture of 6 0 gm (42 0 mMol) 4-dimethylaminocyclohexanone and 9 5 gm (42 0 mMol) 4-bromophenylhydrazine hydrochloride in 100 mL ethanol were added 3 4 mL (42 mMol) pyridine The resultant mixture was then heated at reflux for 2 hours and then stirred at ambient temperature for 18 hours The reaction mixture was then treated with aqueous potassium carbonate and extracted well with dichloromethane The organic phases were combined dried over sodium sulfate and concentrated under reduced pressure The resultant residue was treated with toluene and concentrated again under reduced pressure to give 11 3 gm (87%) of the desired compound

6-bromo-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole hydrochloride

A solution of 11 3 gm (36 4 mMol) 4-dimethylaminocyclohexanone 4-bromophenylhydrazone in 250 mL 4M ethanolic hydrogen chloride were heated to reflux under nitrogen for 3 hours The reaction mixture was allowed to cool to room temperature and was then concentrated under reduced pressure The residual paste was dissolved in 200 mL water and to this solution were then added 50 mL 6 M hydrochloric acid The mixture was cooled to 0°C for 18 hours The desired product which had crystallized was filtered and dried to give 8 66 gm (72%)

Silylation

8 66 gm (26 2 mMol) 6-bromo-3-(dimethyl)amino-1 2,3,4-tetrahydro-9H-carbazole hydrochloride were partitioned between 1N sodium hydroxide and dichloromethane The organic phase was dried over sodium sulfate and concentrated under reduced pressure The residue was dissolved in 50 mL tetrahydrofuran and the resultant solution was added to a suspension of 8 0 gm (40 mMol) potassium hydride (20% in mineral oil) in 100 mL tetrahydrofuran cooled to about 0°C The resultant mixture was stirred for an hour at this temperature and then to it were added 8 0 mL (30 mMol) triisopropylsilyltriflate and the mixture was allowed to warm gradually to room temperature After 18 hours the reaction mixture was treated with ice to decompose excess potassium hydride Once all of the hydride had been destroyed, the reaction mixture was diluted with 200 mL of water and was then extracted well with dichloromethane The organic phases were combined dried over sodium sulfate and concentrated under reduced pressure The residual oil was subjected to silica gel chromatography eluting sequentially with toluene 9 1 toluene ethyl acetate, 4 1 toluene ethyl acetate, 1 1 toluene ethyl acetate and ethyl acetate The ethyl acetate fractions were combined and concentrated under reduced pressure to give 7 08 gm (60%) of the title compound as a solid
m p =92-93°C
NMR($CDCl_3$) δ7 52 (d 1H), 7 39 (dd 1H), 7 13 (d 1H) 3 04 (br dd 1H), 2 88 (m 2H), 2 70 (m 1H), 2 58 (dd 1H), 2 41 (s, 6H) 2 20 (d 1H) 1 78 (m, 3H) 1 70 (m, 1H), 1 14 (m, 18H)

All N-methyl-N-methoxyamides useful for the preparation of the compounds of Formula V are available by substituting an appropriate carboxylic acid for 4-chlorobenzoic acid in the following procedure

Preparation B-II

4-chloro-N-methyl-N-methoxybenzamide

To a solution 11 38 gm (116 7 mMol) N-methoxy-N-methyl amine hydrochloride in 700 mL 1N sodium hydroxide was added a solution of 18 56 gm (106 04 mMol) 4-chlorobenzoyl chloride in 200 mL dichloromethane and the mixture was stirred at ambient temperature After 18 hours the phases were separated and the remaining aqueous was extracted well with dichloromethane All organic phases are combined, dried over sodium sulfate and concentrated under reduced pressure to give 27 9 gm (95%) of the title compound as a clear oil
MS(m/e) 199(M^+)
IR 3011, 2974, 2938, 1634 cm^{-1}

Preparation B-III

6-amino-3-(dimethyl)amino-1,2 3,4-tetrahydro-9H-carbazole hydrochloride

6-(t-butoxycarbonyl)amino-3-(dimethyl)amino-9-trimethylsilyl-1 2,3 4-tetrahydro-9H-carbazole

To a solution of 0 898 gm (2 0 mMol) 6-bromo-3-(dimethyl)amino-9-triisopropylsilyl-1,2 3,4-tetrahydro-9H-carbazole in 20 mL tetrahydrofuran at -70°C were added 1 56 mL (2 2 mMol) n-butyllithium (1 41 M in hexane) The solution was allowed to stir at this temperature for 45 minutes and then it was siphoned over 15 minutes into a solution of 0 50 mL (2 3 mMol) diphenylphosphoryl azide in 20 mL tetrahydrofuran at -70°C The wine red solution was maintained at -70°C for 2 hours at which point the reaction mixture was treated with 2 5 mL (8 9 mMol) sodium bis(2-methoxyethoxy) aluminum hydride (65% in toluene) The reaction mixture was allowed to warm to 0°C during which time gas evolution was observed and the reaction mixture became pale yellow After 30 minutes at 0°C the reaction mixture was allowed to warm to room temperature After 30 minutes at room temperature the reaction mixture was again cooled to 0°C and was cautiously treated with ice to decompose excess hydride The reaction mixture was then filtered to remove the precipitate that had formed and the precipitate was washed thoroughly with diethyl ether The combined filtrates were washed sequentially with dilute aqueous sodium hydroxide and saturated aqueous sodium chloride dried over sodium sulfate and concentrated under reduced pressure to a viscous oil This oil was then dissolved in 10 mL dichloromethane

and to it were added 0 50 gm (2 3 mMol) di-(t-butyl)carbonate The resulting solution was then stirred for 18 hours at room temperature The reaction mixture was then concentrated under reduced pressure The residue was then dissolved in toluene and concentrated under reduced pressure to remove and residual t-butanol The residue was then subjected to column chromatography eluting with a gradient of chloroform (2-8% 95 5 methanol ammonium hydroxide) to give 0 45 gm (46%) of the desired compound as a colorless glass
MS(m/e) 486(M^+)
Calculated for $C_{28}H_{47}N_3OSi$ Theory C 69 23 H 9 75 N 8 65 Found C, 68.93 H, 9 50 N 8 44

6-(t-butoxycarbonyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

To a solution of 0 44 gm (0 91 mMol) 6-(t-butoxycarbonyl)amino-3-(dimethyl)amino-9-triisopropylsilyl-1,2,3,4-tetrahydro-9H-carbazole in 10 mL tetrahydrofuran at 0°C were added 0 30 gm boric acid followed by 1 5 mL 1M aqueous tetrabutylammonium fluoride After 3 hours the reaction mixture was added to dilute aqueous tartaric acid and the resulting mixture extracted several times with dichloromethane The remaining aqueous phase was made basic with dilute aqueous sodium hydroxide and extracted well with dichloromethane This organic phase was dried over sodium sulfate and concentrated under reduced pressure This residue was subjected to radial chromatography (2 mm silica gel) eluting with 96 4 chloroform methanol containing 5% ammonium hydroxide Fractions shown to contain product were combined and concentrated under reduced pressure to give 0 246 gm (83%) of the desired product
MS(m/e) 330(M^+)

Deprotection of 6-amino group

0 385 gm (1 17 mMol) 6-(t-butoxycarbonyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole were dissolved in 10 mL trifluoroacetic acid and the mixture allowed to stir for 1 hour at room temperature The reaction mixture was then concentrated under reduced pressure and the residue dissolved in dichloromethane The organic phase was washed with aqueous potassium carbonate. dried over sodium sulfate and concentrated under reduced pressure to give 0 261 gm (97%) of the title compound as a grayish-tan foam

The phenylhydrazines required for the synthesis of the compounds of Formula V may be prepared by the procedure described in detail in Preparation B-IV

Preparation B-IV

4-(4-fluorobenzoyl)aminophenylhydrazine

4-(4-fluorobenzoyl)aminonitrobenzene

To a suspension of 30 0 gm (0 217 mole) 4-nitroaniline in 225 mL dichloromethane were added 17 57 mL (0 217 mole) pyridine The suspension was cooled to 0°C and then 25 66 mL (0 217 mole) 4-fluorobenzoyl chloride were added slowly Within 15 minutes the reaction mixture became homogeneous and was allowed to warm to room temperature After an hour an additional 2 56 mL (21 7 mMol) 4-fluorobenzoyl chloride and 1 75 mL (21 7 mMol) pyridine were added and the reaction continued at room temperature for an additional hour The reaction mixture was then washed with 200 mL water at which point a precipitate formed The solid was filtered. washed with 100 mL hexane washed with 200 mL water and dried under reduced pressure at 60°C to give 56 6 gm (100%) of the desired compound

4-(4-fluorobenzoyl)aminoaniline

To a solution of 56 6 gm (0 217 mole) 4-(4-fluorobenzoyl)aminonitrobenzene in 875 mL tetrahydrofuran were added 5 7 gm 5% platinum on carbon The reaction mixture was hydrogenated at room temperature for 18 hours at initial hydrogen pressure of 60 p s i The reaction mixture was then filtered and the filtrate concentrated under reduced pressure to give 49 3 gm (98 5%) of the desired compound

Diazotization/Reduction

To a suspension of 1 00 gm (4 34 mMol) 4-(4-fluorobenzoyl)aminoaniline in 4 25 mL concentrated hydrochloric acid at 0°C were added very slowly a solution of 0 329 gm (4 77 mMol) sodium nitrite in 3 2 mL water The mixture was stirred at this temperature for 10 minutes and was then cannulated into a solution of 3 917 gm (17 36 mMol) stannous chloride dihydrate in 4 25 mL concentrated hydrochloric acid at 0°C The resultant suspension was stirred at this temperature for 1 hour The reaction was then treated with 50 mL 5N sodium hydroxide and was extracted well

with ethyl acetate The organic extracts were combined dried over magnesium sulfate and concentrated under reduced pressure to give 0 90 gm (82%) of the title compound
MS(m/e) 245(M^+)

The reaction described in Preparation B-V is representative of the Fischer Indole conditions for the preparation of the compounds of Formula V

Preparation B-V

6-(4-fluorobenzoyl)amino-3-(1-phthalimidyl)-1 2 3 4-tetrahydro-9H-carbazole

A suspension of 0 28 gm (1 11 mMol) 4-(1-phthalimidyl)cyclohexanone and 0 256 gm (1 05 mMol) 4-(4-fluorobenzoyl)aminophenylhydrazine in 8 0 mL ethanol were heated to reflux for 1 hour To this mixture were then added 10 drops concentrated hydrochloric acid The resulting mixture was heated to reflux for 18 hours The reaction mixture was then cooled to room temperature and was diluted with 10 mL diethyl ether followed by 30 mL hexanes The resulting solid was filtered and dried under vacuum to give 0 288 gm of the title compound The filtrate was concentrated under reduced pressure and the residue subjected to silica gel chromatography. eluting with 40 60 5 ethyl acetate hexane methanol. to give an additional 0 128 gm of product Total yield 0 416 gm (87%)

Preparation B-VI

4-(1-phthalimidyl)cycloheptanone

To a stirred solution of 5 00 gm (20 55 mMol) 4-(1-phthalimidyl)cyclohexanone in 30 mL diethyl ether were added 3 79 mL (30 8 mMol) boron trifluoride ethereate After stirring for 20 minutes at room temperature 3 24 mL (30 8 mMol) ethyl diazoacetate were added dropwise The resultant solution was stirred for 16 hours at room temperature The reaction mixture was diluted with saturated aqueous sodium carbonate and was then extracted with diethyl ether The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure The residue was dissolved in 15 mL dimethylsulfoxide To this wolution was added 1 3 mL water and 1 5 gm sodium chloride The resulting mixture was heated at 170°C for 7 hours The reaction mixture was then cooled poured into 150 mL water and extracted well with diethyl ether The combined organic phases were washed sequentially with water and saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure The residue was subjected to silica gel chromatography. eluting with 6 4 hexane ethyl acetate Fractions shown to contain product were combined and concentrated under reduced pressure to give 4 17 gm (79%) of the title compound
MS(m/e) 257(M^+)

Preparation B-VII

7-(benzyloxycarbonyl)amino-3- and 4-(1-phthalimidyl)-cyclohepta[7,6-b]indole

A suspension of 1 09 gm (4,25 mMol) 4-(1-phthalimidyl) cycloheptanone and 1 60 gm (6 2 mMol) 4-(benzyloxycarbonyl) aminophenylhydrazine in 40 0 mL ethanol were heated to reflux for 1 hour To this mixture were then added 0 2 mL concentrated hydrochloric acid The resulting mixture was heated to reflux for 18 hours The reaction mixture was then concentrated under reduced pressure and the residue subjected to silica gel chromatography, eluting with 40% ethyl acetate in hexane Fractions containing product were combined and concentrated under reduced pressure to give 1 61 gm (79%) of the title compound
MS(m/e) 479(M^+)

Preparation B-VIII

6-benzyloxy-3-carboxy-1 2,3,4-tetrahydro-9H-carbazole Ethyl 6-benzyloxy-3-carboxy-1 2 3 4-tetrahydro-9H-carbazole

To a suspension of 3 242 gm (12 93 mMol) 4-benzyloxyphenylhydrazine hydrochloride in 80 mL ethanol were added 1 05 mL (12 93 mMol) pyridine The resulting mixture was heated to 50°C for about 20 minutes and then 1 87 mL (11 75 mMol) ethyl 4-oxocyclohexanecarboxylate were added The resulting mixture was stirred at reflux for 18 hours The reaction mixture was then concentrated under reduced pressure and the residue partitioned between water and ethyl acetate The organic phase was separated washed with water dried over magnesium sulfate and concentrated under reduced pressure The residue was subjected to silica gel chromatography eluting with 35% ethyl acetate

in hexane Fractions containing product were combined and concentrated under reduced pressure to give 3 38 gm (83%) of the desired compound

Hydrolysis

To a suspension of 3 107 gm (8 9 mMol) ethyl 6-benzyloxy-3-carboxy-6-benzyloxy-1 2 3 4-tetrahydro-9H-carbazole in 100 mL 2N sodium hydroxide were added 100 mL methanol and the reaction mixture stirred at reflux for 3 5 hours The reaction mixture was concentrated to about half volume and the pH adjusted to between 5 and 7 by the addition of concentrated hydrochloric acid The mixture was extracted well with 4 1 dichloromethane isopropanol The organic phases were combined dried over sodium sulfate and concentrated under reduced pressure to give 2 71 gm (95%) of the title compound

Preparation B-IX

2-(1-methyl-1H-pyrazol-3-yl)-1-ethanol

To a mixture of 200 gm (2 85 mole) 2 3-dihydrofuran and 800 mL (4 81 mole) triethylorthoformate were added 0 8 mL (6 5 mMol) boron trifluoride diethyl etherate dropwise After an initial exotherm the reaction mixture was allowed to stir at ambient temperature for four days To the reaction mixture was then added 4 0 gm potassium carbonate and the reaction mixture was distilled under 6 0 mm Hg Fractions distilling between 60°C and 130°C were collected to give 261 64 gm (42 1%) of a light yellow oil
MS(m/e) 219(M^+)

To a solution of 87 2 gm (0 40 mole) of the previously prepared yellow oil in 787 mL 1N HCl were added 21 3 mL (0 40 mole) methyl hydrazine and the reaction mixture was stirred at reflux for four hours The reaction mixture was cooled to ambient temperature and the volatiles were removed under reduced pressure The residual oil was treated with 2N NaOH until basic and the aqueous extracted well with dichloromethane The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure to give 32 15 gm (64 5%) of the title compound as a brown oil
MS(m/e) 126(M^+)
^{1}H-NMR(DMSO-d_6) δ7 45 (s 1H) 7 25 (s. 1H) 4 65 (t 1H) 3 75 (s 3H) 3 55 (m. 2H) 2 55 (t 2H)

Preparation B-X

2-(1-isopropyl-1H-pyrazol-3-yl)-1-ethanol

To a solution of 1 0 gm (9 0 mMol) 2-(3-pyrazolyl)-1-ethanol in 36 mL dimethylformamide were added 2 38 gm (22 5 mMol) sodium carbonate followed by the dropwise addition of a solution of 0 89 mL (9 0 mMol) 2-iodopropane in 8 mL dimethylformamide The reaction mixture was heated to 100°C for 18 hours The reaction mixture was then cooled to ambient and then concentrated under reduced pressure The residue was partitioned between water and dichloromethane The organic phase was then washed with water followed by saturated aqueous sodium chloride and was then dried over sodium sulfate The remaining organics were concentrated under reduced pressure to give 0 36 gm (26 0%) of the title compound as a brown oil ^{1}H-NMR(DMSO-d_6) 67 50 (s, 1H), 7 25 (s, 1H), 4 60 (t, 1H), 4 40 (m. 1H) 3 50 (m 2H) 2 55 (t 2H) 1 35(d 6H)

Preparation B-XI

2-(4-chloro)phenyl-1-mesyloxyethane

To a stirring solution of 3 00 mL (22 16 mMol) 2-(4-chloro)phenyl-I-ethanol in 75 mL tetrahydroluran at 0°C were added 4 63 mL (33 24 mMol) triethylamine followed by 1 89 mL (24 38 mMol) methanesulfonyl chloride The reaction mixture was allowed to stir at room temperature for 18 hours The reaction mixture was then poured into water and extracted well with ethyl acetate The organic phases were combined washed with water, dried over sodium sulfate and concentrated under reduced pressure to give 5 18 gm (99 6%) of the title compound

EXAMPLE B-1

6-acetyl-3-(dimethyl)amino-1 2,3 4-tetrahydro-9H-carbazole 6-carboxy-3-(dimethyl)amino-9-triisopropylsilyl-1 2 3 4-tetrahydro-9H-carbazole

To a solution of 2 95 gm (6 56 mMol) 6-bromo-3-(dimethyl)amino-9-triisopropylsilyl-1,2 3 4-tetrahydro-9H-carbazole in 150 mL tetrahydrofuran at -78°C were added 16 4 mL (26 24 mMol) t-butyllithium (1 6 M in pentane) The dark solution was allowed to stir at this temperature for 1 hour and then carbon dioxide gas was bubbled through the solution until the dark color discharged to light yellow After allowing the reaction mixture to warm to room temperature it was poured into water the pH adjusted to about 7, and the mixture extracted well with dichloromethane The organic phases were combined, dried over magnesium sulfate and concentrated under reduced pressure The residue was triturated with hexane to give 2 31 gm (85%) of the desired compound as a tan foam
IR 3022 2958, 2871, 1465 1249 cm^{-1}
MSm/e) 414(M^+)

6-acetyl-3-(dimethyl)amino-6-acetyl-9-triisopropylsilyl-1 2,3 4-tetrahydro-9H-carbazole

To a solution of 2 0 gm (4 8 mMol) 6-carboxy-3-(dimethyl)amino-6-carboxy-9-triisopropylsilyl-1 2 3 4-tetrahydro-9H-carbazole in 100 mL diethyl ether at 0°C were added 8 mL (9 6 mMol) methyllithium (1 2 M in diethyl ether) over a 15 minute period After an hour an additional 0 4 mL of the methyllithium solution were added 0 4 mL additions were continued until all of the starting material had reacted The reaction mixture was then allowed to warm to room temperature and to it was first added ice and then the reaction mixture was diluted with 100 mL of water The mixture was shaken and the phases separated The aqueous phase was twice extracted with 100 mL aliquots of fresh diethyl ether All of the organic extracts were combined, washed with saturated aqueous sodium chloride and concentrated under reduced pressure The residue was subjected to florisil chromatography, eluting sequentially with toluene 9 1 toluene ethyl acetate 4 1 toluene ethyl acetate 1 1 toluene ethyl acetate, and ethyl acetate Fractions containing product were combined and concentrated under reduced pressure to give 1 37 gm (69%) of the desired product as a solid
MS(m/e) 412(M^+)
Calculated for $C_{25}H_{40}N_2OSi$ Theory C, 72 76 H, 9 77 N 6 79 Found C 72 65, H 9 84, N. 6 74

Deprotection

To a solution of 1 37 m (3 29 mMol) 6-acetyl-3-(dimethyl)amino-6-acetyl-9-triisopropylsilyl-1,2,3,4-tetrahydro-9H-carbazole in 25 mL tetrahydrofuran at 0°C containing 1 5 gm boric acid were added 5 mL 1M aqueous tetrabutylammonium fluoride After 1 hour the reaction mixture was added to dilute aqueous tartaric acid and the resulting mixture extracted several times with dichloromethane The remaining aqueous phase was made basic and was then extracted well with dichloromethane This organic phase was dried over sodium sulfate and concentrated under reduced pressure to give a clear oil This oil was crystallized from toluene 0 72 gm (86%) of the title compound as a crystalline solid
m p =181-182°C
MS(m/e) 256(M^+)
Calculated for $C_{16}H_{20}N_2O$ Theory C 74 97, H 7 86, N. 10 93 Found C 74 71, H, 7 91 N. 10 76

EXAMPLE B-2

6-benzoyl-3-(dimethyl)amino-1,2 3,4-tetrahydro-9H-carbazole 6-benzoyl-3-dimethyl)amino-9-triisopropylsilyl-1 2 3,4-tetrahydro-9H-carbazole

To a solution of 0 50 gm (1 11 mMol) 6-bromo-3-(dimethyl)amino-9-triisopropylsilyl-1 2 3 4-tetrahydro-9H-carbazole in 50 mL tetrahydrofuran at -78°C were added 1 96 mL (3 33 mMol) t-butyllithium (1 7 M in pentane) and the resulting dark solution was allowed to stir for 30 minutes To this mixture were then added 0 20 gm (1 22 mMol) N-methyl-N-methoxybenzamide and the reaction mixture was allowed to warm to room temperature over 1 hour The reaction mixture was then treated with 0 1 N sodium hydroxide and then extracted well with chloroform The organic phases were combined, dried over potassium carbonate and concentrated under reduced pressure to give 0 48 gm (91%) of the desired compound as a red-orange oil
MS(m/e) 474(M^+)

Deprotection

To a solution of 1 00 gm (2 11 mMol) 6-benzoyl-3-(dimethyl)amino-9-triisopropylsilyl-1 2 3 4-tetrahydro-9H-carbazole in 50 mL tetrahydrofuran at 0°C were added 5 mL tetrabutylammonium fluoride (1M in tetrahydrofuran) and 3 mL 1N boric acid The reaction mixture was allowed to stir for 1 hour The reaction mixture was then poured into dilute aqueous tartaric acid and the aqueous phase washed with dichloromethane The remaining aqueous phase was made basic and was then extracted well with dichloromethane This organic phase was dried over sodium sulfate and concentrated under reduced pressure The residue was subjected to silica gel chromatography. eluting with dichloromethane containing from 0 to 20% methanol Fractions containing product were combined and concentrated under reduced pressure to give 0 64 gm (96%) of the title compound as a tan foam
MS(m/e) 319(M^+)

The compounds of the following Examples 3-4 were prepared by the procedure described in EXAMPLE B-2

EXAMPLE B-3

6-(4-methoxy)benzoyl-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

Beginning with 1 0 gm (2 22 mMol) 6-bromo-3-(dimethyl)amino-9-triisopropylsilyl-1 2 3 4-tetrahydro-9H-carbazole 0 08 gm (10%) of the title compound were recovered as a yellow foam
MS(m/e) 348(M^+)

EXAMPLE B-4

6-(4-chloro)benzoyl-3-(dimethyl)amino-1 2,3 4-tetrahydro-9H-carbazole

Beginning with 0 5 gm (1 11 mMol) 6-bromo-3-(dimethyl)amino-9-triisopropylsilyl-1.2 3,4-tetrahydro-9H-carbazole, 0 17 gm (43 7%) of the title compound were recovered as a yellow foam
MS(m/e) 352(M^+)

EXAMPLE B-5

6-(methoxycarbonyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

To a mixture of 6 0 mg (0 026 mMol) 6-amino-3-(dimethyl)amino-1.2,3 4-tetrahydro-9H-carbazole and 8 0 mg (07 mMol) polyvinylpyridine in 3 0 mL dichloromethane were added 2 4 mg (0 0273 mMol) methyl chloroformate The reaction mixture was mixed for 2 days at ambient temperature To this mixture were then added 90 mg (0 073 mMol) aminomethylated polystyrene and the reaction mixed for an additional 18 hours The reaction mixture was then filtered and the volatiles evaporated to give 4 0 mg (53%) of the title compound
MS(m/e) 268(M^+)

The compounds of the following Examples 6-8 were prepared by the procedure described in detail in EXAMPLE B-5

EXAMPLE B-6

6-(ethoxycarbonyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

Beginning with 6 0 mg (0 026 mMol) 6-amino-3-(dimethyl)amino-1 2,3,4-tetrahydro-9H-carbazole and 2 96 mg (0 0273 mMol) ethyl chloroformate 4 1 mg (52%) of the title compound were recovered
MS(m/e) 302(M^+)

EXAMPLE B-7

6-(allyloxycarbonyl)amino-3-(dimethyl)amino-1 2,3 4-tetrahydro-9H-carbazole

Beginning with 10 0 mg (0 0437 mMol) 6-amino-3-(dimethyl)amino-1,2 3 4-tetrahydro-9H-carbazole and 5 5 mg (0 0458 mMol) allyl chloroformate. 4 4 mg (33%) of the title compound were recovered
MS(m/e) 313(M^+)

EXAMPLE B-8

6-(4-fluorophenoxycarbonyl)amino-3-(dimethyl)amino-1 2,3,4-tetrahydro-9H-carbazole

Beginning with 6 0 mg (0 026 mMol) 6-amino-3-(dimethyl)amino-1 2 3,4-tetrahydro-9H-carbazole and 4 8 mg (0 0273 mMol) 4-fluorophenyl chloroformate 3 8 mg (40%) of the title compound were recovered
MS(m/e) 368 (M^+)

EXAMPLE B-9

N-methyl-N'-(3-(dimethyl)amino-1 2,3,4-tetrahydro-9H-carbazol-6-yl)thiourea

To a solution of 10 0 mg (0 0437 mMol) 6-amino-3-(dimethyl)amino-1,2,3,4-tetrahydro-9H-carbazole in 3 0 mL dichloromethane were added 6 2 mg (0 0874 mMol) methyl isothiocyanate The reaction was mixed for 48 hours and to it were then added 0 15 gm (0 0874 mMol) aminomethylated polystyrene and the reaction mixed for an additional 18 hours The reaction mixture was then filtered and the volatiles evaporated to give 6 3 mg (48%) of the title compound
MS(m/e) 302(M^+)

The compounds of the following Examples 10-11 were prepared according to the procedure described in detail in EXAMPLE B-9

EXAMPLE B-10

N-phenyl-N'-(3-(dimethyl)amino-1,2,3,4-tetrahydro-9H-carbazol-6-yl)thiourea

Beginning with 10 0 mg (0 0437 mMol) 6-amino-3-(dimethyl)amino-1,2,3,4-tetrahydro-9H-carbazole and 11 8 mg (0 0874 mMol) phenyl isothiocyanate 7 2 mg (39%) of the title compound were recovered
MS(m/e) 364(M^+)

EXAMPLE B-11

N-(2,3-dichloro)phenyl-N'-(3-(dimethyl)amino-1,2,3 4-tetrahydro-9H-carbazol-6-yl)thiourea

Beginning with 10 0 mg (0 0437 mMol) 6-amino-3-(dimethyl)amino-1,2,3,4-tetrahydro-9H-carbazole and 17 8 mg (0 0874 mMol) 2,3-dichlorophenyl isothiocyanate. 6 1 mg (33%) of the title compound were recovered
MS(m/e) 432 (M^+)

EXAMPLE B-12

N-ethyl-N'-(3-(dimethyl)amino-1 2,3,4-tetrahydro-9H-carbazol-6-yl)urea

To a solution of 10 0 mg (0 0437 mMol) 6-amino-3-(dimethyl)amino-1 2,3,4-tetrahydro-9H-carbazole in 3 0 mL dichloromethane were added 6 2 mg (0 0874 mMol) ethyl isocyanate The reaction was mixed for 46 hours and to it were then added 0 15 gm (0 0874 mMol) aminomethylated polystyrene and the reaction mixed for an additional 18 hours The reaction mixture was then filtered and the filtrate washed with 1N hydrochloric acid The aqueous phase was washed several times with dichloromethane and was then made basic with dilute aqueous sodium hydroxide The aqueous phase was then extracted several times with an equal volume of dichloromethane These organic extracts were dried over sodium sulfate and then concentrated under reduced pressure to give 3 0 mg (23%) of the title compound
MS(m/e) 300(M^+)

EXAMPLE B-13

N-phenyl-N'-(3-(dimethyl)amino-1 2 3,4-tetrahydro-9H-carbazol-6-yl)urea

Beginning with 10 0 mg (0 0437 mMol) 6-amino-3-(dimethyl)amino-1,2 3,4-tetrahydro-9H-carbazole and 10 4 mg (0 0874 mMol) phenyl isocyanate. 1 0 mg (7%) of the title compound was recovered using the procedure described in detail in EXAMPLE B-12
MS(m/e) 348(M^+)

EXAMPLE B-14

6-(3-methylbutanoyl)amino-3-(dimethyl)amino-6-(3-methylbutanoyl)amino-1 2,3 4-tetrahydro-9H-carbazole hydrochloride

To a solution of 0 25 gm (1 091 mMol) 6-amino-3-(dimethyl)amino-1 2.3 4-tetrahydro-9H-carbazole and 115 µL (1 418 mMol) pyridine in 15 mL dichloromethane at 0°C were added 0 160 mL (1 309 mMol) isovaleryl chloride The reaction mixture was allowed to warm to room temperature After about 40 minutes the reaction was partitioned between dichloromethane and 2N sodium hydroxide The phases were separated and the organic phase was washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure The residue was subjected to silica gel chromatography, eluting with dichloromethane containing 15% methanol and 1 5% ammonium hydroxide Fractions shown to contain product were combined and concentrated under reduced pressure The residue was converted to the hydrochloride salt which was crystallized from ethanol/diethyl ether to give 0 208 gm (54%) of the title compound

m p =171°C (decomp)

Calculated for $C_{19}H_{27}N_3O$•HCl Theory C 65 22 H 8 07 N 12 01 Found C 64 94 H 8 12 N 11 90

The compounds of the following Examples 15-19 are prepared by the procedure described in detail in EXAMPLE B-14

EXAMPLE B-15

6-(propanoyl)amino-3-(dimethyl)amino-6-(propanoyl)amino-1 2 3 4-tetrahydro-9H-carbazole hydrochloride

Beginning with 0 25 gm (1 091 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 0 114 mL (1 309 mMol) propanoyl chloride 0 268 gm of the title compound were recovered

m p =279°C (decomp)

Calculated for $C_{17}H_{23}N_3O$•HCl Theory C 63 44 H 7 52 N 13 06 Found C, 63 24 H 7 65. N 13 09

EXAMPLE B-16

6-(2-methylprop-1-en-3 -oyl)amino-3-(dimethyl)amino-1 2 3.4-tetrahydro-9H-carbazole hydrobromide

Beginning with 0 046 gm (0 20 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 0 023 mL (0 24 mMol) 2-methylprop-1-en-3-oyl chloride 0 035 gm (59%) of 6-(2-methylprop-1-en-3-oyl)amino-3-(dimethyl)amino-1 2.3 4-tetrahydro-9H-carbazole were recovered and then treated with hydrogen bromide to give the title compound

m p =236-238°C

MS(m/e) 297(M^+)

EXAMPLE B-17

6-(cyclopropanoyl)amino-3-(dimethyl)amino-1,2.3 4-tetrahydro-9H-carbazole hydrobromide

Beginning with 0 169 gm (0 74 mMol) 6-amino-3-(dimethyl)amino-1 2.3,4-tetrahydro-9H-carbazole and 0 077 mL (0 85 mMol) cyclopropanoyl chloride 0 195 gm (89%) of 6-(cyclopropanoyl)amino-3-(dimethyl)amino-1 2 3.4-tetrahydro-9H-carbazole were recovered and then treated with hydrogen chloride to give the title compound

m p =216-218°C

MS(m/e) 297(M^+)

Calculated for $C_{18}H_{23}N_3O$•HCl Theory C. 64 76 H 7 25 N 12 59 Found C 64 52 H 7 13 N 12 35

EXAMPLE B-18

6-(cyclobutanoyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole hydrobromide

Beginning with 0 169 gm (0 74 mMol) 6-amino-3-(dimethyl)amino-1 2.3,4-tetrahydro-9H-carbazole and 0 097 mL (0 85 mMol) cyclobutanoyl chloride 0 230 gm (99%) of 6-(cyclobutanoyl)amino-3-(dimethyl)amino-1 2 3.4-tetrahydro-9H-carbazole were recovered and then treated with hydrogen chloride to give the title compound

m p =214-216°C

MS(m/e) 311(M^+)

EXAMPLE B-19

6-(cyclohexanoyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole hydrobromide

Beginning with 0 132 gm (0 58 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 0 085 mL (0 635 mMol) cyclohexanoyl chloride 0 173 gm (88%) of 6-(cyclohexanoyl)amino-3-(dimethyl)amino-1,2.3 4-tetrahydro-9H-carbazole were recovered and then treated with hydrogen chloride to give the title compound
m p =224-226°C
MS(m/e) 340(M^+)
Calculated for $C_{21}H_{29}N_3O \cdot HCl$ Theory C 67 09 H 8 04 N 11 17 Found C 66 89 H 7 74 N 11 40

EXAMPLE B-20

6-(4-chlorobenzoyl)amino-3-(dimethyl)amino-1 2 3,4-tetrahydro-9H-carbazole

To a mixture of 10 6 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 14 0 mg (0 12 mMol) polyvinylpyridine in 3 0 mL dichloromethane were added 8 8 µL (0 069 mMol) 4-chlorobenzoyl chloride The reaction mixture was mixed for 1 day at ambient temperature To this mixture were then added 160 mg (0 128 mMol) aminomethylated polystyrene and the reaction mixed for an additional 18 hours The reaction mixture was diluted with 1 0 mL methanol treated with potassium carbonate, and filtered through a short column of sodium sulfate The filtrate was then evaporated to give 2 9 mg (17%) of the title compound as a beige solid
MS(m/e) 367(M^+)

The compounds of the following Examples 21-51 were prepared by the procedure described in detail in EXAMPLE B-20

EXAMPLE B-21

6-(4-methoxybenzoyl)amino-3-(dimethyl)amino-1.2,3.4-tetrahydro-9H-carbazole

Beginning with 10 6 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2.3 4-tetrahydro-9H-carbazole and 8 8 µL (0 063 mMol) 4-methoxybenzoyl chloride 6 9 mg (41%) of the title compound were recovered as a light brown foam
MS(m/e) 363(M^+)

EXAMPLE B-22

6-(3-chlorobenzoyl)amino-3-(dimethyl)amino-1 2,3,4-tetrahydro-9H-carbazole

Beginning with 10 6 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2 3,4-tetrahydro-9H-carbazole and 8 8 µL (0 063 mMol) 3-chlorobenzoyl chloride. 4 2 mg (25%) of the title compound were recovered as a brown solid
MS(m/e) 367(M^+)

EXAMPLE B-23

6-(3-methoxybenzoyl)amino-3-(dimethyl)amino-1 2,3.4-tetrahydro-9H-carbazole

Beginning with 10 6 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2.3,4-tetrahydro-9H-carbazole and 8 8 µL (0 063 mMol) 3-methoxybenzoyl chloride 9 8 mg (59%) of the title compound were recovered as a brown foam
MS(m/e) 363(M^+)

EXAMPLE B-24

6-(2-thienoyl)amino-3-(dimethyl)amino-1 2,3 4-tetrahydro-9H-carbazole

Beginning with 10 6 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2 3,4-tetrahydro-9H-carbazole and 8 8 µL (0 082 mMol) 2-thienoyl chloride 9 7 mg (62%) of the title compound were recover d as a brown solid
MS(m/e) 339(M^+)

EXAMPLE B-25

6-(2-fluorobenzoyl)amino-3-idimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 5 4 mg (0 051 mMol) 2-fluorobenzoyl chloride, 11 6 mg (74%) of the title compound were recovered as a beige solid MS(m/e) 351(M^+)

EXAMPLE B-26

6-(2-chlorobenzoyl)amino-3-(dimethyl)amino-1 2,3,4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 5 7 mg (0 051 mMol) 2-chlorobenzoyl chloride 12 3 mg (73%) of the title compound were recovered as a beige solid MS(m/e) 367(M^+)

EXAMPLE B-27

6-(2-methoxybenzoyl)amino-3-(dimethyl)amino-1 2,3 4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2,3,4-tetrahydro-9H-carbazole and 8 6 uL (0 051 mMol) 2-methoxybenzoyl chloride, 13 4 mg (80%) of the title compound were recovered as a beige solid MS(m/e) 367(M^+)

EXAMPLE B-28

6-(2-methylbenzoyl)amino-3-(dimethyl)amino-1 2,3 4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1,2 3 4-tetrahydro-9H-carbazole and 8 9 µL (0 051 mMol) 2-methylbenzoyl chloride 11 3 mg (71%) of the title compound were recovered as a beige solid MS(m/e) 347(M^+)

EXAMPLE B-29

6-(3-methylbenzoyl)amino-3-(dimethyl)amino-1.2 3 4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1.2 3 4-tetrahydro-9H-carbazole and 8 9 µL (0 051 mMol) 3-methylbenzoyl chloride, 12 3 mg (77%) of the title compound were recovered as a beige solid MS(m/e) 347(M^+)

EXAMPLE B-30

6-(4-methylbenzoyl)amino-3-(dimethyl)amino-1.2 3,4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 8 9 µL (0 051 mMol) 4-methylbenzoyl chloride 14 6 mg (91%) of the title compound were recovered as a beige solid MS(m/e) 347(M^+)

EXAMPLE B-31

6-(2 3-difluorobenzoyl)amino-3-(dimethyl)amino-1 2,3 4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 8 6 µL (0 051 mMol) 2 3-difluorobenzoyl chloride 13 4 mg (79%) of the title compound were recovered as a b ige solid MS(m/e) 369(M^+)

EXAMPLE B-32

6-(2 4-difluorobenzoyl)amino-3-(dimethyl)amino-1 2.3.4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2,3.4-tetrahydro-9H-carbazole and 8 6 µL (0 051 mMol) 2 4-difluorobenzoyl chloride, 13 8 mg (81%) of the title compound were recovered as a beige solid MS(m/e) 369(M^+)

EXAMPLE B-33

6-(2 5-difluorobenzoyl)amino-3-(dimethyl)amino-1 2,3 4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2,3,4-tetrahydro-9H-carbazole and 8 6 uL (0 051 mMol) 2.5-difluorobenzoyl chloride, 13 3 mg (78%) of the title compound were recovered as a beige solid MS(m/e) 369(M^+)

EXAMPLE B-34

6-(3,4-difluorobenzoyl)amino-3-(dimethyl)amino-1,2,3.4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2 3.4-tetrahydro-9H-carbazole and 8 6 µL (0 051 mMol) 3 4-difluorobenzoyl chloride, 7 2 mg (42%) of the title compound were recovered as a beige solid MS(m/e) 369(M^+)

EXAMPLE B-35

6-(3 5-difluorobenzoyl)amino-3-(dimethyl)amino-1,2,3.4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1.2 3,4-tetrahydro-9H-carbazole and 8 6 µL (0 051 mMol) 3 5-difluorobenzoyl chloride, 6 2 mg (36%) of the title compound were recovered as a beige solid MS(m/e) 369(M^+)

EXAMPLE B-36

6-(2,3-dichlorobenzoyl)amino-3-(dimethyl)amino-1,2 3 4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1,2,3.4-tetrahydro-9H-carbazole and 9 5 mg (0 051 mMol) 2 3-dichlorobenzoyl chloride, 14 1 mg (76%) of the title compound were recovered as a brown solid MS(m/e) 401(M^+)

EXAMPLE B-37

6-(1-naphthoyl)amino-3-(dimethyl)amino-1,2,3.4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 10 2 µL (0 051 mMol) 1-naphthoyl chloride 13 8 mg (76%) of the title compound were recovered as a dark brown solid MS(m/e) 383(M^+)

EXAMPLE B-38

6-(2-naphthoyl)amino-3-(dimethyl)amino-1,2,3 4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2 3,4-tetrahydro-9H-carbazole and 10 2 µL (0 051 mMol) 2-naphthoyl chloride 12 6 mg (72%) of the title compound were recovered as a dark brown solid MS(m/e) 383(M^+)

EXAMPLE B-39

6-(4-phenylbenzoyl)amino-3-(dimethyl)amino-1 2 3,4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 15 mg (0 051 mMol) 4-phenylbenzoyl chloride 13 4 mg (71%) of the title compound were recovered as a brown solid MS(m/e) 409(M^+)

EXAMPLE B-40

6-(2-thionaphthoyl)amino-3-(dimethyl)amino-1,2,3,4-tetrahydro9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 14 mg (0 051 mMol) 2-thionaphthoyl chloride 14 8 mg (83%) of the title compound were recovered as a dark brown solid MS(m/e) 369(M^+)

EXAMPLE B-41

6-(phenylacetyl)amino-3-(dimethyl)amino-1 2,3 4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 8 1 uL (0 051 mMol) phenylacetyl chloride 13 6 mg (85%) of the title compound were recovered as a grey-brown solid MS(m/e) 348(M+1)

EXAMPLE B-42

6-(2-thienylacetyl)amino-3-(dimethyl)amino-1 2 3,4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1,2,3 4-tetrahydro-9H-carbazole and 8 1 µL (0 051 mMol) 2-thienylacetyl chloride, 13 7 mg (84%) of the title compound were recovered as a dark brown solid MS(m/e) 354(M+1)

EXAMPLE B-43

6-(3-fluorobenzoyl)amino-3-(dimethyl)amino-1 2,3 4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2,3 4-tetrahydro-9H-carbazole and 8 1 uL (0 051 mMol) 3-fluorobenzoyl chloride, 10 8 mg (69%) of the title compound were recovered as a beige solid MS(m/e) 352(M+1)

EXAMPLE B-44

6-(4-bromobenzoyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 14 7 mg (0 051 mMol) 4-bromobenzoyl chloride 3 6 mg (20%) of the title compound were recovered as a light beige solid MS(m/e) 413(M^+)

EXAMPLE B-45

6-(4-iodobenzoyl)amino-3-(dimethyl)amino-1 2,3 4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 17 9 mg (0 051 mMol) 4-iodobenzoyl chloride, the title compound was recovered as a light beige solid MS(m/e) 459(M^+)

EXAMPLE B-46

6-(2 4-dichlorobenzoyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2.3 4-tetrahydro-9H-carbazole and 9 5 µL (0 051 mMol) 2 4-dichlorobenzoyl chloride 12 8 mg (72%) of the title compound were recovered as a light beige solid
MS(m/e) 401(M+)

EXAMPLE B-47

6-(benzenesulfonyl)amino-3-(dimethyl)amino-1 2 3,4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 8 6 µL (0 051 mMol) benzenesulfonyl chloride. 5 6 mg (34%) of the title compound were recovered as a light beige solid
MS(m/e) 370(M+)

EXAMPLE B-48

6-(4-fluorobenzenesulfonyl)amino-3-(dimethyl)amino-1 2,3 4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2.3 4-tetrahydro-9H-carbazole and 13 1 mg (0 067 mMol) 4-fluorobenzenesulfonyl chloride the title compound was recovered as a light beige solid
MS(m/e) 388(M+)

EXAMPLE B-49

6-(4-methylbenzenesulfonyl)amino-3-idimethyl)amino-1,2,3,4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2 3.4-tetrahydro-9H-carbazole and 12 8 mg (0 067 mMol) 4-methylbenzenesulfonyl chloride 5 3 mg (31%) of the title compound were recovered as a light beige solid
MS(m/e) 383(M+)

EXAMPLE B-50

6-(4-chlorobenzenesulfonyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 14 1 mg (0 067 mMol) 4-chlorobenzenesulfonyl chloride, 11 5 mg (64%) of the title compound were recovered as a light beige solid
MS(m/e) 403(M+)

EXAMPLE B-51

6-(4-iodobenzenesulfonyl)amino-3-(dimethyl)amino-1.2 3.4-tetrahydro-9H-carbazole

Beginning with 10 4 mg (0 046 mMol) 6-amino-3-(dimethyl)amino-1 2 3.4-tetrahydro-9H-carbazole and 20 3 mg (0 067 mMol) 4-iodobenzenesulfonyl chloride 10 3 mg (47%) of the title compound were recovered as a light beige solid
MS(m/e) 495(M+)

EXAMPLE B-52

6-(4-fluorobenzoyl)amino-3-(dimethyl)amino-1 2 3,4-tetrahydro-9H-carbazole oxalate hemihydrate

A solution of 0 10 gm (0 30 mMol) 6-(t-butoxycarbonyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole in 1 0 mL trifluoroacetic acid was stirred for 20 minutes at room temperature The reaction mixture was then concentrated under reduced pressure The residual oil was then dissolved in 5 mL tetrahydrofuran To this solution was added

1 5 mL triethylamine followed by 5 0 µL (0 42 mMol) 4-fluorobenzoyl chloride and the solution was stirred for 1 hour at room temperature The reaction mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane This solution was washed with aqueous potassium carbonate and was then concentrated under reduced pressure The residue was dissolved in dilute aqueous tartaric acid and the solution was extracted well with dichloromethane The remaining aqueous phase was made basic with dilute aqueous sodium hydroxide and was extracted well with dichloromethane These organic phases were combined dried over sodium sulfate and concentrated under reduced pressure The residue was subjected to silica gel chromatography eluting with 95 5 chloroform 5% ammonium hydroxide in methanol Fractions containing the product were combined and concentrated under reduced pressure to give 0 102 gm (95%) of 6-(4-fluorobenzoyl)amino-3-(dimethyl)amino-1 2 3,4-tetrahydro-9H-carbazole
MS(m/e) 351(M^+)
Calculated for $C_{21}H_{22}N_3OF$ Theory C 71 27 H 6 31 N 11 96 Found C 71 47 H 6 32 N 11 86

A solution of 0 82 mg (0 23 mMol) 6-(4-fluorobenzoyl)amino-3-(dimethyl)amino-1 2 3,4-tetrahydro-9H-carbazole in 1 mL ethyl acetate were added to a solution of 0 21 mg (0 23 mMol) oxalic acid in 1 mL ethyl acetate The solid which formed was filtered washed with ethyl acetate and dried to give 0 77 mg (75%) of the title compound
m p >150°C (decomp)

The compounds of Examples 53-55 were prepared by the procedure described in detail in EXAMPLE B-52

EXAMPLE B-53

6-(benzoyl)amino-3-(dimethyl)amino-1,2,3.4-tetrahydro-9H-carbazole

Beginning with 0 198 gm (0 60 mMol) 6-(t-butoxycarbonyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 9 7 µL (0 84 mMol) benzoyl chloride 0 075 gm (38%) of the title compound were prepared as a light grey foam
MS(m/e) 333(M^+)
Calculated for $C_{21}H_{23}N_3O$ Theory C 75 65 H. 6 95 N 12 60 Found C 75 35 H 6 97 N, 12 50

EXAMPLE B-54

6-(2-furoyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole oxalate hemihydrate

Beginning with 0 10 gm (0 30 mMol) 6-(t-butoxycarbonyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 5 0 µL (0 51 mMol) 2-furoyl chloride 0 080 gm (82%) of 6-(2-furoyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole were prepared
MS(m/e) 323(M^+)
Calculated for $C_{19}H_{21}N_3O_2$ Theory C 70 57 H 6 54 N 12 99 Found C 70 29 H 6 54 N 12 99

0 063 gm (0 20 mMol) of 6-(2-furoyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole were treated with oxalic acid to give 0 052 gm (64%) ofthe title compound
m p >110°C (decomp)

EXAMPLE B-55

6-(2-chloro-4-fluorobenzoyl)amino-3-(dimethyl)amino-1 2 3,4-tetrahydro-9H-carbazole

Beginning with 0 081 gm (0 245 mMol) 6-(t-butoxycarbonyl)amino-3-(dimethyl)amino-1,2 3 4-tetrahydro-9H-carbazole and 0 046 gm (0 27 mMol) 2-chloro-4-fluorobenzoyl chloride 0 089 gm (94%) of the title compound were recovered as a light beige solid
MS(m/e) 385(M^+)
IR(KBr) 3626 3472 3427 2975 2962 2786. 1666 1603 1478 cm^{-1}
Calculated for $C_{21}H_{21}N_3OClF$ Theory C 65 37 H 5.49 N 10 89 Found C 65 17 H 5 50 N 10 73

EXAMPLE B-56

6-(indol-5-oyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole hydrochloride

To a solution of 43 5 mg (0 27 mMol) indole-5-carboxylic acid in 1 5 mL dimethylformamide were added 44 3 mg (0 27 mMol) carbonyldiimidazole resulting in immediate gas evolution The reaction mixture was stirred for 4 hours at room temperature and then 60 0 mg (0 26 mMol) 6-amino-3-(dimethyl)amino-1,2 3,4-tetrahydro-9H-carbazole were added After 3 days the reaction mixture was concentrated under reduced pressure The residue was subjected to

silica gel chromatography eluting with 4 1 dichloromethane 2% ammonium hydroxide in methanol Fractions shown to contain product were combined and concentrated under reduced pressure to give 66 7 mg (69%) of 6-(indol-5-oyl) amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole The compound was converted to its corresponding hydrochloride salt crystallizing from ethanol diethyl ether

m p =235-237°C

Exact Mass Calculated for $C_{23}H_{25}N_4O$ Theory 373 2028, Found 373 2042

EXAMPLE B-57

6-(4-fluorobenzoyl)amino-3-amino-1 2 3 4-tetrahydro-9H-carbazole hydrochloride

To a solution of 0 187 gm (0 41 mMol) 6-(4-fluorobenzoy)amino-3-(1-phthalimido)-1 2 3 4-tetrahydro-9H-carbazole in 6 mL ethanol and 1 5 mL water were added 0 45 mL hydrazine monohydrate and the reaction mixture was stirred at room temperature After 12 hours the reaction mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate and saturated aqueous sadium carbonate The organic phase was washed with water dried over sodium sulfate and concentrated under reduced pressure The residue was subjected to silica gel chromatography Fractions shown to contain product were combined and concentrated under reduced pressure to give 0 101 gm (76%) of 6-(4-fluorobenzoyl)amino-3-amino-1 2 3 4-tetrahydro-9H-carbazole The compound was converted to its corresponding hydrochloride salt, crystallizing from ethanol diethyl ether m p =252-255°C

MS(m/e) 323(M^+)

Calculated for $C_{19}H_{18}N_3OF \cdot HCl$ Theory C 63 42, H 5 32, N, 11 68 Found C 63 20, H, 5 57 N. 11 91

EXAMPLE B-58

6-(4-fluorobenzoyl)amino-3-(ethyl)amino-1 2,3 4-tetrahydro-9H-carbazole hydrobromide and 6-(4-fluorobenzoyl) amino-3-(diethyl)amino-1 2 3 4-tetrahydro-9H-carbazole hydrochloride

To a solution of 0 194 gm (0 60 mMol) 6-(4-fluorobenzoyl)amino-3-amino-1,2,3 4-tetrahydro-9H-carbazole in 15 mL ethanol were added 300 mg Raney Nickel and the reaction mixture heated to reflux After 2 hours the reaction mixture was filtered through a pad of celite The pad was washed with 400 mL of methanol and the filtrates were concentrated under reduced pressure The residue was subjected to silica gel chromatography, eluting with 100 10 3 dichloromethane methanol ammonium hydroxide Fractions containing the first eluting product were combined and concentrated under reduced pressure to give 137 3 mg (60 3 %) of 6-(4-fluorobenzoyl)amino-3-(diethyl)amino-1 2,3 4-tetrahydro-9H-carbazole The corresponding hydrochloride salt was prepared

m p =222-224°C

Exact Mass Calculated for $C_{23}H_{27}N_3OF$ Theory 380 2138 Found 380 2144

Fractions containing the second eluting spot were combined and concentrated under reduced pressure to give 0 033 gm (16%) of 6-(4-fluorobenzoyl)amino-3-(ethyl)amino-1,2 3 4-tetrahydro-9H-carbazole The corresponding hydrobromide salt was prepared

m p =226-230°C

Exact Mass Calculated for $C_{21}H_{23}N_3OF$ Theory 352 1825 Found 352 1825

EXAMPLE B-59

6-(4-fluorobenzoyl)amino-3-(2-phenylethyl)amino-1,2,3,4-tetrahydro-9H-carbazole hydrochloride

To a mixture of 0 568 gm (1 758 mMol) 6-(4-fluorobenzoyl)amino-3-amino-1,2 3,4-tetrahydro-9H-carbazole, 0 485 gm (3 512 mMol) potassium carbonate and 0 316 gm (2 109 mMol) sodium iodide in 10 mL acetonitrile were added 0 288 mL (2 109 mMol) 2-phenyl-1 -ethyl bromide and the reaction mixture was heated at reflux for 5 hours The reaction mixture was then cooled to room temperature and partitioned between dichloromethane and water The aqueous phase was extracted well with dichloromethane The dichloromethane phases were combined, dried over magnesium sulfate and concentrated under reduced pressure The residue was subjected to silica gel chromatography, eluting with 97 2 5 0 5 dichloromethane methanol ammonium hydroxide Fractions shown to contain product were combined and concentrated under reduced pressure to give 0 543 gm (72 3%) 6-(4-fluorobenzoyl)amino-3-(2-phenethyl)amino-1 2 3 4-tetrahydro-9H-carbazole The corresponding hydrochloride salt was prepared to provide the title compound

m p 207-208°C

Calculated for $C_{27}H_{26}N_3OF \cdot HCl$ Theory C, 68 89, H 5 87 N 9 06 Found C 68 69 H, 6 07 N 8 94

EXAMPLE B-60

6-(4-fluorobenzoyl)amino-3-[2-(4-fluorophenyl)ethyl]amino-1 2 3 4-tetrahydro-9H-carbazole hydrochloride

Beginning with 0 601 gm (1 560 mMol) 6-(4-fluorobenzoyl)amino-3-amino-1 2 3 4-tetrahydro-9H-carbazole and 0 525 gm (2 405 mMol) 2-(4-fluorophenyl)-1-mesyloxyethane 0 270 gm (32 8%) of the title compound were prepared by the procedure described in EXAMPLE B-31
m p 210-211°C
Calculated for $C_{27}H_{25}N_3OF_2$•HCl Theory C 67 29 H 5 44 N 8 72 Found C 67 05 H 5 61 N 8 45

EXAMPLE B-61

6-(4-fluorobenzoyl)amino-3-(2-(1-methyl-1H-pyrazol-4-yl)ethyl)amino-1 2 3 4-tetrahydro-9H-carbazole hydrochloride

To a mixture of 0 40 gm (1 24 mMol) 6-(4-fluorobenzoyl)amino-3-amino-1 2 3 4-tetrahydro-9H-carbazole and 0 257 gm (1 86 mMol) potassium carbonate in 8 0 mL dimethylform-amide were added 0 303 gm (1 49 mMol) 2-(1-methyl-1H-pyrazol-4-yl)-1-mesyloxyethane in 2 0 mL dimethylformamide and the mixture was stirred at 60-75°C for 18 hours An additional 0 101 gm (0 50 mMol) 2-(1-methyl-1H-pyrazol-4-yl)-1-mesyloxyethane were added and the reaction heated to 150°C After 1 5 hours the reaction mixture was cooled to room temperature and was then partitioned between water and dichloromethane The aqueous phase was extracted again with dichloromethane The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure The residue was subjected to silica gel chromatography eluting with 95 5 0 5 dichloromethane methanol ammonium hydroxide Fractions shown to contain product were combined and concentrated under reduced pressure to give 0 180 gm (33 6%) of 6-(4-fluorobenzoyl) amino-3-(2-(1-methyl-1H-pyrazol-4-yl)ethyl)amino-1,2,3 4-tetrahydro-9H-carbazole The corresponding hydrochloride salt was prepared to provide the title compound m p =185-190°C
Exact Mass Calculated for $C_{25}H_{26}N_5OF$ Theory 432 2202 Found 432 2200

EXAMPLE B-62

3-(2-(1-isopropyl-1H-pyrazol-4-yl)ethyl)amino-6-(4-fluorobenzoyl)amino-1 2 3 4-tetrahydro-9H-carbazole hydrochloride

Beginning with 0 400 gm (1 24 mMol) 6-(4-fluorobenzoyl)amino-3-amino-1,2 3 4-tetrahydro-9H-carbazole and 0 346 gm (1 49 mMol) 2-(1-methyl-1H-pyrazol-3-yl)-1-mesyloxyethane 0 0632 gm (10 3%) of the title compound were prepared by the procedure described in EXAMPLE B-33
Exact Mass Calculated for $C_{27}H_{30}N_5OF$ Theory 460 2513 Found 460 2491

EXAMPLE B-63

6-hydroxy-3-amino-1 2,3,4-tetrahydro-9H-carbazole

To a solution of 0 871 gm (2 98 mMol) 6-benzyloxy-3-amino-1 2 3 4-tetrahydro-9H-carbazole in 200 mL ethanol were added about 2 0 gm Raney Nickel and hydrogen introduced to the reaction mixture under balloon pressure After stirring for 18 hours at room temperature the balloon was refilled with hydrogen and the reaction stirred an additional 3 days at room temperature The reaction mixture was filtered and the filtrate concentrated under reduced pressure to give a colorless solid The residual solid was subjected to silica gel chromatography. eluting with 80 15 5 dichloromethane methanol ammonium hydroxide Fractions shown to contain product were combined and concentrated under reduced pressure to give 0 335 gm (56%) of the title compound
m p =230°C (decomp)
Calculated for $C_{12}H_{14}N_2O$ Theory C 71 26 H. 6 98. N 13 85 Found C 71 00. H 7 01. N, 13 70

EXAMPLE B-64

6-hydroxy-3-(methyl)amino-1 2 3 4-tetrahydro-9H-carbazole 6-benzyloxy-3-(t-butyloxycarbonyl)amino-1 2 3 4-tetrahydro-9H-carbazole

To a solution of 1 00 gm (3 42 mMol) 6-benzyloxy-3-amino-1 2 3 4-tetrahydro-9H-carbazole in 30 mL tetrahydrofuran were added 1 79 mL 2N sodium hydroxide followed by 0 784 gm (3 59 mMol) di(t-butyl)dicarbonate The reaction

mixture was stirred at room temperature for about 45 minutes and was then concentrated under reduced pressure The residue was dissolved in dichloromethane and washed well with water The remaining organics were dried over magnesium sulfate and concentrated under reduced pressure to give 1 339 gm (99%) of the desir d compound

6-benzyloxy-3-(methyl)amino-1 2.3 4-tetrahydro-9H-carbazole

A solution of 1 35 gm (3 44 mMol) 6-benzyloxy-3-(t-butyloxycarbonyl)amino-1 2 3.4-tetrahydro-9H-carbazole in 15 mL tetrahydrofuran were added dropwise over 30-40 minutes to a suspension of 0 46 gm (12 04 mMol) lithium aluminum hydride in 30 mL tetrahydrofuran at 0°C The reaction mixture was allowed to stir at this temperature for 20 minutes after the addition was complete and was then warmed to 75°C for 4 5 hours The reaction mixture was then cooled to room temperature and treated with sodium sulfate decahydrate The mixture was cooled to 0°C and was then filtered The solid collected was washed sequentially with tetrahydrofuran and dichloromethane and the combined filtrates were concentrated under reduced pressure The residue was subjected to silica gel chromatography eluting with ethyl acetae Fractions shown to contain product were combined and concentrated under reduced pressure to 0 797 gm (76%) of the desired product
m p =146-147°C
Calculated for $C_{20}H_{22}N_2O$ Theory C. 78 40. H. 7 24 N. 9 16 Found C. 78 53. H. 7 36. N. 9 14

Hydrogenolysis

Beginning with 0 522 gm (1 70 mMol) 6-benzyloxy-3-(methyl)amino-1,2 3,4-tetrahydro-9H-carbazole, 0 226 mg (61%) of the title compound were recovered as described in EXAMPLE B-35
m p =120-121°C
Exact Mass Calculated for $C_{13}H_{16}N_2O$ Theory 217 1341 Found. 217 1336

EXAMPLE B-65

6-hydroxy-3-(ethyl)amino-1.2.3,4-tetrahydro-9H-carbazole 6-benzyloxy-3-(ethyl)amino-1.2.3 4-tetrahydro-9H-carbazole

To a solution of 0 225 gm (0 77 mMol) 6-benzyloxy-3-amino-1,2.3,4-tetrahydro-9H-carbazole in 20 mL acetonitrile were added 0 223 gm (1 617 mMol) potassium carbonate followed by 130 µL (1 617 mMol) iodoethane and the reaction mixture was stirred at room temperature for 18 hours The reaction mixture was then heated at 60°C for 4 hours and then at 50-45°C for 3 hours The reaction mixture was then concentrated under reduced pressure and the residue partitioned between dichloromethane and water The organic phase was then dried over magnesium sulfate and concentrated under reduced pressure The residue was subjected to radial chromatography (silica gel, 2 mm) eluting with 97 3 1 dichloromethane methanol ammonium hydroxide Fractions shown to contain the desired compound were concentrated under reduced pressure to give 0 045 gm (6%) of the desired compound
Exact Mass Calculated for $C_{21}H_{25}N_2O$ Theory 321 1967 Found 321 1970

Hydrogenolysis

Beginning with 0 492 gm (1 536 mMol) 6-benzyloxy-3-(ethyl)amino-1,2 3,4-tetrahydro-9H-carbazole 0 271 mg (76 6%) of the title compound were recovered as described in EXAMPLE B-35
m p =117-118°C
Exact Mass Calculated for $C_{14}H_{18}N_2O$ Theory 231 1497 Found 231 1490

EXAMPLE B-66

6-hydroxy-3-(propyl)amino-1 2.3 4-tetrahydro-9H-carbazole hydrochloride

6-benzyloxy-3-(propyl)amino-1 2,3.4-tetrahydro-9H-carbazole

To a solution of 0 600 gm (2 05 mMol) 6-benzyloxy-3-amino-1,2.3.4-tetrahydro-9H-carbazole in 35 mL acetonitrile were added 0 283 gm (2 05 mMol) potassium carbonate followed by 240 µL (2 46 mMol) iodopropane and the reaction mixture was stirred at room temperature for 2 5 days Additional iodopropane was added and the reaction stirred at room temperature until all of the starting material had been consumed The reaction mixture was then partitioned between dichloromethane and water The aqueous phase was extracted with dichloromethane and the combined or-

ganic phases were then dried over magnesium sulfate and concentrated under reduced pressure The residue was subjected to silica gel chromatography eluting with 96 5 3 0 5 dichloromethane isopropanol ammonium hydroxide Fractions shown to contain the desired compound were concentrated under reduced pressure to give 0 270 gm (39%) of the desired compound

Hydrogenolysis

To a solution of 0 27 gm 6-benzyloxy-3-(propyl)amino-1 2 3 4-tetrahydro-9H-carbazole in 50 mL ethanol were added 100 mg 5% palladium on carbon and the reaction mixture was hydrogenated at room temperature for 1.6 hours with an initial hydrogen pressure of 60 p s i The reaction mixture was then filtered through celite washing the filter pad well with methanol The combined filtrates were concentrated under reduced pressure The residue was subjected to silica gel chromatography, eluting with 90 9 1 dichloromethane methanol ammonium hydroxide Fractions shown to contain product were combined and concentrated under reduced pressure to give 0 083 gm (42%) of the title compound The corresponding hydrochloride salt was formed and crystallized from methanol/diethyl ether
m p =105°C (decomp)
Exact Mass Calculated for $C_{15}H_{20}N_2O$ Theory 245 1654 Found 245 1659

The compounds of the following Examples 67-68 were prepared by the procedure described in detail in EXAMPLE B-66

EXAMPLE B-67

6-hydroxy-3-(diethyl)amino-1 2 3 4-tetrahydro-9H-carbazole hydrochloride

Beginning with 1 00 gm (2 05 mMol) 6-benzyloxy-3-amino-1 2 3 4-tetrahydro-9H-carbazole and 820 µL (10 27 mMol) iodoethane 0 0382 gm (10%) of 6-hydroxy-3-(diethyl)amino-1 2 3.4-tetrahydro-9H-carbazole were recovered The hydrochloride salt was prepared to give the title compound m p =271-271°C
Exact Mass Calculated for $C_{16}H_{22}N_2O$ Theory 259 1810 Found 259 1816

EXAMPLE B-68

6-hydroxy-3-(dipropyl)amino-1 2 3,4-tetrahydro-9H-carbazole hydrochloride

Beginning with 1 00 gm (2 05 mMol) 6-benzyloxy-3-amino-1 2 3 4-tetrahydro-9H-carbazole and 1 67 mL (17 11 mMol) 1-iodopropane 0 200 gm (70%) of 6-hydroxy-3-(dipropyl)amino-1 2,3 4-tetrahydro-9H-carbazole were recovered The hydrochloride salt was prepared to give the title compound
Calculated for $C_{18}H_{26}N_2O \cdot HCl$ Theory C. 66 96 H 8 43 N. 8 68 Found C 56 69 H. 8 25 N 8 90

EXAMPLE B-69

6-hydroxy-3-(2-phenyleth-1-yl)amino-1 2 3,4-tetrahydro-9H-carbazole hydrochloride

6-benzyloxy-3-(2-phenyleth-1-yl)amino-1 2,3 4-tetrahydro-9H-carbazole

To a solution of 0 32 gm (1 1 mMol) 6-benzyloxy-3-amino-1 2 3 4-tetrahydro-9H-carbazole in 8 mL acetonitrile were added 0 30 gm (1 68 mMol) potassium carbonate 0 25 gm (1 68 mMol) sodium iodide and 0 23 mL (1 68 mMol) 2-phenyl-1-ethyl bromide The resulting mixture was stirred 4 hours at room temperature followed by 5 hours at reflux The reaction mixture was cooled to room temperature and then partitioned between dichloromethane and water The aqueous phase was extracted well with dichloromethane All of the organic phases were combined, dried over magnesium sulfate and concentrated under reduced pressure The residue was subjected to silica gel chromatography, eluting with 7% methanol in dichloromethane Fractions shown to contain product were concentrated under reduced pressure to give 0 345 gm (79%) of the desired compound A portion was converted to the corresponding hydrochloride salt. m p =242-244°C (ethanol/diethyl ether)

Hydrogenolysis

Beginning with 0 336 gm (0 85 mMol) 6-benzyloxy-3-(2-phenyleth-1-yl)-amino-1 2 3,4-tetrahydro-9H-carbazole 0 175 gm (67%) of 6-hydroxy-3-(2-phenylethyl)amino-1 2 3 4-tetrahydro-9H-carbazole were prepared by the procedure described in detail in EXAMPLE B-35 The hydrochloride salt was prepared and crystallized from ethanol/diethyl

ether to give the title compound
m p =178-180°C
MS(m/e) 307(M^+)
Calculated for $C_{20}H_{22}N_2O$•HCl Theory C, 70 06 H 6 76, N 8 17 Found C, 70 32 H 6 78 N 8 22

EXAMPLE B-70

6-hydroxy-3-(2-(4-fluorophenyl)eth-1-yl)amino-1 2,3.4-tetrahydro-9H-carbazole hydrochloride

6-benzyloxy-3-(2-(4-fluorophenyl)eth-1-yl)amino-1 2 3 4-tetrahydro-9H-carbazole

Beginning with 1 00 gm (3 422 mMol) 6-benzyloxy-3-amino-1,2,3,4-tetrahydro-9H-carbazole and 1 274 gm (5 82 mMol) 2-(4-fluorophenyl)-1-mesyloxyethane, 0 896 gm (63%) of 6-benzyloxy-3-(2-(4-fluorophenyl)eth-1-yl)amino-1 2,3.4-tetrahydro-9H-carbazole were recovered by the procedure described in detail in EXAMPLE B-33 A portion was converted to the corresponding hydrochloride salt and crystallized from ethanol/diethyl ether
m p =244-245°C
Calculated for $C_{27}H_{27}N_2OF$•HCl Theory C 71 91, H, 6 26 N 6 21 Found C 71 70 H. 6 26 N 6 09

Hydrogenolysis

To a solution of 0 700 gm (1 69 mMol) 6-benzyloxy-3-(2-(4-fluorophenyl)eth-1-yl)amino-1 2.3.4-tetrahydro-9H-carbazole in 50 mL methanol were added 1 07 gm (16 90 mMol) ammonium formate followed by 0 190 gm 5% palladium on carbon The resulting mixture was stirred at reflux for 15 minutes The reaction mixture was then filtered through a bed of celite and the filter cake washed well with methanol The combined filtrates were concentrated under reduced pressure and the residue partitioned between water and dichloromethane The phases were separated and the aqueous was extracted again with 4 1 isopropanol dichloromethane The combined extracts were dried over magnesium sulfate, concentrated under reduced pressure and the residue subjected to silica gel chromatography, eluting with 91 8 1 dichloromethane methanol ammonium hydroxide Fractions shown to contain product were combined and concentrated under reduced pressure to give 0 245 gm (52%) of 6-hydroxy-3-(2-(4-fluorophenyl)eth-1-yl)amino-1,2 3,4-tetrahydro-9H-carbazole The hydrochloride salt was prepared and crystallized from ethanol/diethyl ether to give the title compound
m p =160°C (decomp)
Calculated for $C_{20}H_{21}N_2OF$•HCl Theory C 66 57, H 6 14 N, 7 76 Found C, 66 34, H, 6 14, N, 7 59

EXAMPLE B-71

6-benzyloxy-3-(2-(4-chlorophenyl)eth-1-yl)amino-1,2.3,4-tetrahydro-9H-carbazole hydrochloride

Beginning with 1 00 gm (3 422 mMol) 6-benzyloxy-3-amino-1,2 3,4-tetrahydro-9H-carbazole and 1 371 gm (5 82 mMol) 2-(4-chlorophenyl)-1-mesyloxyethane 0 833 gm (56%) of 6-benzyloxy-3-(2-(4-chlorophenyl)eth-1-yl)amino-1 2,3.4-tetrahydro-9H-carbazole were recovered by the procedure described in detail in EXAMPLE B-33 A portion was converted to the corresponding hydrochloride salt and crystallized from ethanol/diethyl ether
m p =238-240°C
Calculated for $C_{27}H_{27}N_2OCl$•HCl Theory C, 68 38 H, 6 04, N, 5 99 Found C 68 63, H, 6 17 N 6 05

EXAMPLE B-72

6-hydroxy-3-(2-(1-methyl-1H-pyrazol-4-yl)ethyl)amino-1,2.3.4-tetrahydro-9H-carbazole hydrochloride

6-benzyloxy-3-(2-(1-methyl-1H-pyrazol-4-yl)ethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

To a solution of 1 00 gm (3 422 mMol) 6-benzyloxy-3-amino-1,2 3,4-tetrahydro-9H-carbazole in 50 mL acetonitrile were added 1 04 gm (7 53 mMol) potassium carbonate followed by 1 26 gm (6 16 mMol) 2-(1-methyl-1H-pyrazol-4-yl)-1-mesyloxyethane and th reaction mixture was heated to reflux for 18 hours To the reaction mixture were then added 0 021 gm (0 171 mMol) 4-dimethylaminopyridine and reflux was continued for 36 additional hours The reaction mixture was cooled to room temperature and then partitioned between dichloromethane and water The aqueous phase was extracted well with dichloromethane All of the organic phases were combined dried over magnesium sulfate and concentrated under reduced pressure The residue was subjected to silica gel chromatography eluting with 2 5%

methanol in dichloromethane containing 0 5 % ammonium hydroxide Fractions shown to contain product were concentrated under reduced pressure to give 0 610 gm (44%) of the desired compound

Hydrogenolysis

Beginning with 0 610 gm (1 524 mMol) 6-benzyloxy-3-(2-(1-methyl-1H-pyrazol-4-yl)ethyl)amino-1 2 3 4-tetrahydro-9H-carbazole 0 245 gm (52%) of 6-hydroxy-3-(2-(1-methyl-1H-pyrazol-4-yl)ethyl)amino-1 2 3 4-tetrahydro-9H-carbazole were prepared by the hydrogenolysis procedure described in detail in EXAMPLE B-42 The hydrochloride salt was prepared and crystallized from ethanol/diethyl ether to give the title compound
m p =266°C (decomp)
Calculated for $C_{18}H_{21}N_4O\cdot HCl$ Theory C, 62 33 H 6 68 N, 16 15 Found C, 62 54 H, 6 71 N 16 20

EXAMPLE B-73

6-hydroxy-3-(2-(1-isopropyl-1H-pyrazol-4-yl)ethyl)amino-1 2 3 4-tetrahydro-9H-carbazole hydrochloride

6-benzyloxy-3-(2-(1-isopropyl)-1H-pyrazol-4-yl)ethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

Beginning with 0 698 gm (2 39 mMol) 6-benzyloxy-3-amino-1 2 3 4-tetrahydro-9H-carbazole and 0 787 gm (3 39 mMol) 2-(1-isopropyl-1H-pyrazol-4-yl)-1-mesyloxyethane 0 649 gm (63 4%) of the desired compound were prepared by the procedure described in detail in EXAMPLE B-72
MS(m/e) 428(M^+)
A portion of the material was converted to its corresponding hydrochloride salt m p =258-260°C (ethanol/diethyl ether)

Hydrogenolysis

Beginning with 0 532 gm (1 24 mMol) 6-benzyloxy-3-(2-(1-isopropyl-1H-pyrazol-4-yl)ethyl)amino-1 2 3 4-tetrahydro-9H-carbazole 0 322 gm (77%) of 6-hydroxy-3-(2-(1-isopropyl-1H-pyrazol-4-yl)ethyl)amino-1 2 3 4-tetrahydro-9H-carbazole were prepared by the hydrogenolysis procedure described in detail in EXAMPLE B-42 The hydrochloride salt was prepared and crystallized from ethanol/diethyl ether to give the title compound
m p =251-253°C
MS(m/e) 338(M^-)
Calculated for $C_{20}H_{26}N_4O\cdot HCl$ Theory C 64 07 H, 7 26 N 14 94 Found C, 64 29 H 7 28 N 15 17

EXAMPLE B-74

N-methyl-N-(2-phenyleth-1-yl)-6-hydroxy-3-amino-1 2,3 4-tetrahydro-9H-carbazole hydrochloride

N-methyl-N-(2-phenyleth-1-yl)-6-benzyloxy-3-amino-1 2 3,4-tetrahydro-9H-carbazole

To a solution of 0 30 gm (0 98 mMol) 6-benzyloxy-3-(methyl)amino-1 2 3,4-tetrahydro-9H-carbazole in 15 mL acetonitrile were added 0 271 (1 96 mMol) potassium carbonate 0 177 gm (1 18 mMol) sodium iodide and 0 161 mL (1 18 mMol) 2-phenyl-1-ethyl bromide The reaction mixture was heated to reflux for 18 hours At this time an additional 0 07 mL (0 49 mMol) 2-phenyl-1-ethyl bromide were added and reflux was continued for 4 hours The reaction mixture was cooled to room temperature and then partitioned between dichloromethane and water The aqueous phase was extracted well with dichloromethane All organic phases were combined dried over magnesium sulfate and concentrated under reduced pressure The residue was subjected to radial chromatography (4 mm silica gel) eluting with 4 5% methanol in dichloromethane containing 0 55% ammonium hydroxide Fractions containing product were combined and concentrated under reduced pressure to give 0 324 gm (80 6%) of the desired compound

Hydrogenolysis

Beginning with 0 324 gm (0 79 mMol) N-methyl-N-(2-phenyleth-1-yl)-6-benzyloxy-3-amino-1 2 3 4-tetrahydro-9H-carbazole. 0 205 gm (78%) of N-methyl-N-(2-phenylethyl)-6-hydroxy-3-amino-1 2 3 4-tetrahydro-9H-carbazole were prepared by the hydrogenolysis procedure described in detail in EXAMPLE B-70 The hydrochloride salt was prepared and crystallized from ethanol/diethyl ether to give the title compound
m p =159-160°C
Calculated for $C_{21}H_{24}N_2O\cdot HCl$ Theory C 70 67 H 7 06 N 7 85 Found C 70 41 H 7 05 N 7 83

EXAMPLE B-75

N-methyl-N-(2-(4-fluorophenyl)eth-1-yl)-6-hydroxy-3-amino-1 2,3 4-tetrahydro-9H-carbazole hydrochloride

N-methyl-N-(2-(4-fluorophenyl)eth-1-yl)-6-benzyloxy-3-amino-1 2,3 4-tetrahydro-9H-carbazole

Beginning with 0 30 gm (0 98 mMol) 6-benzyloxy-3-(methyl)amino-1,2 3 4-tetrahydro-9H-carbazole in 15 mL acetonitrile and 0 406 mg (1 96 mMol) 2-(4-fluorophenyl)-1-mesyloxyethane, 0 262 gm (62%) of the desired compound were recovered by the procedure described in detail in EXAMPLE B-46

Hydrogenolysis

Beginning with 0 262 gm (0 61 mMol) N-methyl-N-(2-(4-fluorophenyl)eth-1-yl)-6-benzyloxy-3-amino-1,2 3 4-tetrahydro-9H-carbazole 0 183 gm (88%) of N-methyl-N-(2-(4-fluorophenyl)eth-1-yl)-3-amino-6-hydroxy-1,2,3,4-tetrahydro-9H-carbazole were prepared by the hydrogenolysis procedure described in detail in EXAMPLE B-70 The hydrochloride salt was prepared and crystallized from ethanol/diethyl ether to give the title compound
m p =165-166°C
Calculated for $C_{21}H_{23}N_2OF \cdot HCl$ Theory C, 67 28 H 6 45, N, 7 47 Found C 67 48, H, 6 64, N, 7 52

EXAMPLE B-76

N-methyl-N-(2-(1-isopropyl-1H-pyrazol-4-yl)ethyl)-6-hydroxy-3-amino-1 2,3,4-tetrahydro-9H-carbazole hydrochloride

N-methyl-N-(2-(1-isopropyl-1H-pyrazol-4-yl)ethyl)-6-benzyloxy-3-amino-1,2,3,4-tetrahydro-9H-carbazole

Beginning with 0 202 gm (0 66 mMol) 6-benzyloxy-3-(methyl)amino-1 2 3,4-tetrahydro-9H-carbazole in 15 mL acetonitrile and 0 284 mg (1 22 mMol) 2-(1-isopropyl-1H-pyrazol-4-yl)-1-mesyloxyethane, 0 253 gm (87%) of the desired compound were recovered by the procedure described in detail in EXAMPLE B-74.
MS(m/e) 442(M^+)
A portion was converted to the corresponding hydrochloride salt m p =134-136°C (ethanol/diethyl ether)

Hydrogenolysis

Beginning with 0 196 gm (0 44 mMol) N-methyl-N-(2-(1-isopropyl-1H-pyrazol-4-yl)ethyl)-6-benzyloxy-3-amino-1 2 3,4-tetrahydro-9H-carbazole, 0 120 gm (77%) of N-methyl-N-(2-(1-isopropyl-1H-pyrazol-4-yl)ethyl)-6-hydroxy-3-amino-1,2 3,4-tetrahydro-9H-carbazole were prepared by the hydrogenolysis procedure described in detail in EXAMPLE B-70 The hydrochloride salt was prepared and crystallized from ethanol/diethyl ether to give the title compound
m p =184-186°C
MS(m/e) 352(M^+)
Calculated for $C_{21}H_{28}N_4O \cdot HCl$ Theory C 64 85, H, 7 52, N, 14 40 Found C 65 08 H 7 52, N 14 46

EXAMPLE B-77

7 -(4-fluorobenzoyl)amino-4-amino-10H-cyclohepta[7,6-b]indole

To a solution of 0 854 gm (1 827 mMol) of a mixture of 7-(4-fluorobenzoyl)amino-3- and 4-(1-phthalimidoyl)-10H-cyclohepta[7 6-b]indole in 50 mL ethanol were added 3 5 mL hydrazine hydrate and 12 mL water The mixture was stirred at room temperature for 18 hours The reaction mixture was then concentrated under reduced pressure and the residue subjected to silica gel chromatography, eluting with 84 15 1 dichloromethane methanol ammonium hydroxide Fractions containing the desired compound were combined and concentrated under reduced pressure to give 0 196 gm (32%) of the title compound
m p =121-122°C
Exact Mass Calculated for $C_{20}H_{21}N_3OF$ Theory 338 1669 Found 338 1679

EXAMPLE B-78

7-(4-fluorobenzoyl)amino-4-(dimethyl)amino-10H-cyclohepta[7 6-b]indole hydrochloride

To a solution of 0 165 gm (0 489 mMol) 7-(4-fluorobenzoyl)amino-4-amino-10H-cyclohepta[7 6-b]indole in 15 mL tetrahydrofuran were added 1 96 mL (3 9 mMol) 2N sodium hydroxide followed by 104 µL (1 223 mMol) methyl mesylate and the resulting mixture was stirred at room temperature for 18 hours The reaction mixture was diluted with 100 mL dichloromethane and was then washed with 1N sodium hydroxide The remaining organics were dried over magnesium sulfate and then concentrated under reduced pressure The residue was subjected to radial chromatography (silica gel 1 mm) eluting with 88 5 10 1 5 dichloromethane methanol ammonium hydroxide Fractions containing the desired compound were concentrated under reduced pressure to give 0 035 gm (19%) 7-(4-fluorobenzoyl)amino-4-(dimethyl) amino-10H-cyclohepta[7 6-b]indole The corresponding hydrochloride salt was prepared to give the title compound
m p =198°C
Exact Mass Calculated for $C_{22}H_{25}N_3OF$ Theory 366 1982 Found 366 1991

EXAMPLE B-79

7-(benzyloxycarbonyl)amino-4-amino-10H-cyclohepta[7 6-b]indole hydrochloride

Beginning with 1 61 gm (3 36 mMol) of a mixture of 7-(benzyloxycarbonyl)amino- 3- and 4-(1-phthalimidoyl)-10H-cyclohepta[7 6-b]indole, 0 527 gm (44 9%) 7-(benzyloxycarbonyl)amino-4-amino-10H-cyclohepta[7 6-b] indole were prepared by the procedure described in detail in EXAMPLE B-49 The corresponding hydrochloride salt was prepared to give the title compound
m p =201-203°C
MS(m/e) 350(M^+)

EXAMPLE B-80

7-(benzyloxycarbonyl)amino-4-(dimethyl)amino-10H-cyclohepta[7,6-b]indole hydrobromide

To a solution of 0 276 gm (0 79 mMol) 7-(benzyloxycarbonyl)amino-4-amino-10H-cyclohepta[7 6-b]indole in 10 mL acetonitrile were added 0 22 mL (1 5 mMol) triethylamine followed by 0 10 mL (1 6 mMol) iodomethane and the resulting solution stirred for 2 hours at room temperature To the mixture were then added 3 2 mL (6 4 mMol) 2N sodium hydroxide and the reaction stirred for 48 hours at room temperature The reaction mixture was then partitioned between dichloromethane and water The organic phase was dried over sodium sulfate and concentrated under reduced pressure The residue was subjected to silica gel chromatography, eluting with 88 10 2 dichloromethane methanol ammonium hydroxide Fractions containing product were combined and concentrated under reduced pressure to give 0 056 gm (19%) 7-(benzyloxycarbonyl)amino-4-(dimethyl)-amino-10H-cyclohepta[7,6-b] indole The corresponding hydrobromide salt was prepared to give the title compound
m p =91-93°C
Exact Mass Calculated for $C_{23}H_{28}N_3O_2$ Theory 378 2182 Found 378 2199

EXAMPLE B-81

7-hydroxy-4-amino-10H-cyclohepta[7 6-b]indole

7-benzyloxy-4-amino-10H-cyclohepta[7,6-b]indole

Beginning with 1 19 gm (2 73 mMol) of a mixture of 7-benzyloxy- 3- and 4-(1-phthalimidoyl)-10H-cyclohepta[7,6-b] indole, 0 334 gm (40%) 7-benzyloxy-4-amino-10H-cyclohepta[7 6-b]indole were prepared by the procedure described in detail in EXAMPLE B-78

Hydrogenolysis

Beginning with 0 166 gm (0 54 mMol) 7-benzyloxy-4-amino-10H-cyclohepta[7 6-b]indole 0 054 gm (46%) of the title compound were prepared by the procedure described in detail in EXAMPLE B-63
m p =215°C (d comp)
Exact Mass Calculated for $C_{13}H_{17}N_2O$ Theory 217 1341 Found 217 1306

EXAMPLE B-82

7-hydroxy-4-(methyl)amino-10H-cyclohepta[7 6-b]indole hydrochloride

7-benzyloxy-4-(t-butyloxycarbonyl)amino-10H-cyclohepta[7 6-b]indole

To a solution of 1 08 gm (3 52 mMol) 7-benzyloxy-4-amino-10H-cyclohepta[7 6-b]indole in 30 mL tetrahydrofuran were added 1 85 mL 2N sodium hydroxide followed by 0 808 gm (3 7 mMol) di(t-butyl)dicarbonate and the mixture was stirred for 1 hour at room temperature The reaction mixture was concentrated under reduced pressure and the residue partitioned between dichloromethane and water The organic phase was separated, dried over sodium sulfate and concentrated unde reduced pressure The residue was subjected to silica gel chromatography, eluting with 30% hexane in ethyl acetate Fractions containing product were combined and concentrated under reduce pressure to give 1 37 gm (96%) of the desired compound

7-benzyloxy-4-(methyl)amino-10H-cyclohepta[7 6-b]indole

A solution of 1 37 gm (3 37 mMol) 7-benzyloxy-4-(t-butyloxycarbonyl)amino-10H-cyclohepta[7 6-b]indole in 15 mL tetrahydrofuran was added dropwise over 30 minutes to a suspension of 0 47 gm (12 4 mMol) lithium aluminum hydride in 30 mL tetrahydrofuran at 0°C After the addition was complete, the reaction mixture was stirred for 30 minutes at room temperature and then for 4 hours at reflux The reaction mixture was cooled to room temperature and then to it was added sodium sulfate decahydrate until no more gas evolution was observed The resulting suspension was filtered and the filter cake washed with dichloromethane The combined filtrates were concentrated under reduced pressure and the residue subjected to silica gel chromatography, eluting with 10% methanol in dichloromethane containing 0 5% ammonium hydroxide Fractions containing product were combined and concentrated under reduced pressure to give 0 97 gm (90%) of the desired compound

Hydrogenolysis

Beginning with 0 233 gm (0 73 mMol) 7-benzyloxy-4-(methyl)amino-10H-cyclohepta[7,6-b]indole. 0 104 gm (62%) of 7-hydroxy-4-(methyl)amino-10H-cyclohepta[7,6-b]indole were prepared by the procedure described in detail in EXAMPLE B-73 The corresponding hydrochloride was prepared and crystallized from ethanol/diethyl ether to give the title compound m p =262°C (decomp)
Exact Mass Calculated for $C_{14}H_{19}N_2O$ Theory 231 1497 Found 231 1487

EXAMPLE B-83

7-hydroxy-4-(dimethyl) amino-10H-cyclohepta[7 6-b]indole hydrochloride

7-benzyloxy-4-(dimethyl)amino-10H-cyclohepta[7,6-b]indole

Beginning with 0 483 gm (1 5 mMol) 7-benzyloxy-4-(methyl)amino-10H-cyclohepta[7,6-b]indole 0 410 gm (82%) of the desired product were prepared by the acylation/hydride reduction sequence described in detail in EXAMPLE B-82

Hydrogenolysis

Beginning with 0 405 gm (1 21 mMol) 7-benzyloxy-4-(dimethyl)amino-10H-cyclohepta[7 6-b]indole 0 305 gm (90%) of 7-hydroxy-4-(dimethyl)amino-10H-cyclohepta [7,6-b]indoles were prepared by the procedure described in detail in EXAMPLE B-63 The corresponding hydrochloride was prepared and crystallized from ethanol/diethyl ether to give the title compound
m p =186-194°C
Exact Mass Calculated for $C_{15}H_{21}N_2O$ Theory 245 1654 Found 245 1655

EXAMPLE B-84

7-hydroxy-4-(ethyl)amino-10H-cyclohepta[7 6-b]indole hydrochloride

Beginning with 0 288 gm (0 94 mMol) 7-benzyloxy-4-amino-10H-cyclohepta[7 6-b]indole. 0 140 gm (69%) of 7-hy-

droxy-4-(ethyl)-amino-10H-cyclohepta[7 6-b]indole were prepared by the procedure described in detail in EXAMPLE B-35 except that the reaction mixture was heated to 60°C during the course of the reaction The corresponding hydrochloride was prepared and crystallized from ethanol/diethyl ether to give the title compound
m p =270°C (decomp)
MS(m/e) 245(M+)
Calculated for $C_{15}H_{20}N_2O \cdot HCl$ Theory C 64 16 H 7 54 N 9 98 Found C 64 46 H 7 54 N 9 94

EXAMPLE B-85

N N-diethyl-6-hydroxy-3-aminomethyl-1 2 3 4-tetrahydro-9H-carbazole hydrochloride

N,N-diethyl-6-benzyloxy-3-carboxamido-1,2 3 4-tetrahydro-9H-carbazole

To a solution of 0 322 gm (1 00 mMol) 6-benzyloxy-3-carboxy-1 2 3 4-tetrahydro-9H-carbazole in 2 5 mL tetrahydrofuran at 0°C were added a solution of 96 0 µL (1 10 mMol) oxalyl chloride in 1 5 mL tetrahydrofuran dropwise followed by 73 µL (0 90 mMol) pyridine The reaction mixture was allowed to stir at room temperature for 3 hours The reaction mixture was then concentrated under reduced pressure and the residue redissolved in 15 mL tetrahydrofuran This solution was then cooled to 0°C and to it was added a solution of 145 uL diethylamine in 1 5 mL tetrahydrofuran dropwise The resulting solution was stirred at room temperature for 18 hours The reaction mixture was then partitioned between saturated aqueous potassium carbonate and dichloromethane The organic phase was washed well with 2N sodium hydroxide dried over magnesium sulfate and concentrated under reduced pressure The residue was subjected to silica gel chromatography eluting with 98 2 dichloromethane methanol Fractions containing product were combined and concentrated under reduced pressure to give 0 155 gm (41%) of the desired compound

N N-diethyl-6-benzyloxy-3-aminomethyl-6-benzyloxy-1 2 3 4-tetrahydro-9H-carbazole

A solution of 0 368 gm (0 978 mMol) N N-diethyl-6-benzyloxy-3-carboxamido-1 2 3 4-tetrahydro-9H-carbazole in 15 mL tetrahydrofuran were added dropwise to a suspension of 56 0 mg (1 47 mMol) lithium aluminum hydride in 10 mL tetrahydrofuran at 0°C The reaction was stirred for 2 5 hours at room temperature after the addition was complete The reaction mixture was then again cooled to 0°C and 100 mg sodium sulfate decahydrate were added After 2 hours the reaction mixture was diluted with dichloromethane dried over magnesium sulfate and concentrated under reduced pressure to give the desired compound

hydrogenolysis

Beginning with 0 354 gm (0 978 mMol) N,N-diethyl-6-benzyloxy-3-aminomethyl-1 2 3,4-tetrahydro-9H-carbazole, 0 145 gm (55%) of N N-diethyl-6-hydroxy-3-aminomethyl-1 2,3,4-tetrahydro-9H-carbazole were prepared by the procedure described in detail in EXAMPLE B-63 The corresponding hydrochloride salt was prepared to give the title compound
m p =240°C (decomp)
Calculated for $C_{17}H_{24}N_2O \cdot HCl$ Theory C 66 11 H 8 16 N. 9 07 Found C 66 38 H. 8 27 N 8 81

EXAMPLE B-86

N-methyl-6-hydroxy-3-aminomethyl-1 2 3 4-tetrahydro-9H-carbazole hydrochloride

Beginning with 1 00 gm 6-benzyloxy-3-carboxy-1 2,3 4-tetrahydro-9H-carbazole 0 195 gm (27%) of N-methyl-6-hydroxy-3-aminomethyl-1 2 3 4-tetrahydro-9H-carbazole were prepared by the procedure described in detail in EXAMPLE B-85 The corresponding hydrochloride salt was prepared to give the title compound
m p =145-146°C
Exact Mass Calculated for $C_{14}H_{18}N_2O$ Theory 231 1497 Found 231 1485

EXAMPLE B-87

N,N-dimethyl-6-hydroxy-3-aminomethyl-1 2 3 4-tetrahydro-9H-carbazole

Beginning with 1 00 gm 6-benzyloxy-3-carboxy-1 2 3 4-tetrahydro-9H-carbazole 0 141 gm (18%) of the title compound were prepared by the procedure described in detail in EXAMPLE B-85

m p =107-108°C
Calculated for $C_{15}H_{20}N_2O$ Theory C, 73 73 H 8 25 N. 11 47 Found C 73 95 H 8 49 N 11 32

EXAMPLE B-88

N N-dipropyl-6-hydroxy-3-aminomethyl-1 2 3 4-tetrahydro-9H-carbazole hydrochloride

Beginning with 1 00 gm 6-benzyloxy-3-carboxy-1 2 3 4-tetrahydro-9H-carbazole. 0 096 gm (10%) of N.N-dipropyl-6-hydroxy-3-aminomethyl-1 2 3 4-tetrahydro-9H-carbazole were prepared by the procedure described in detail in EXAMPLE B-85 The corresponding hydrochloride salt was prepared to give the title compound
m p =261-263°C (decomp)
Calculated for $C_{19}H_{28}N_2O \cdot HCl$ Theory C, 67 74. H, 8 68 N, 8 31 Found C 67 51 H, 8 77 N 8 22

EXAMPLE B-89

N-ethyl-N-propyl-6-hydroxy-3-aminomethyl-1,2,3 4-tetrahydro-9H-carbazole hydrochloride

Beginning with 0 811 gm 6-benzyloxy-3-carboxy-1 2,3 4-tetrahydro-9H-carbazole, 0 189 gm (16%) of N-ethyl-N-propyl-6-hydroxy-3-aminomethyl-1 2 3 4-tetrahydro-9H-carbazole were prepared by the procedure described in detail in EXAMPLE B-85. except that the hydrogenolysis was performed at 50°C The corresponding hydrochloride salt was prepared to give the title compound
m p >220°C (decomp)
MS(m/e) 286(M^+)
Calculated for $C_{18}H_{26}N_2O \cdot HCl$ Theory C, 66 96. H. 8 43. N. 8 68 Found C 66 66 H. 8 24. N, 8 60

General procedure for the coupling of carboxylic acids with 6-amino-3-(dimethyl)amino-1 2,3 4-tetrahydro-9H-carbazole

To a suspension of 4-5 equivalents of polymer bound 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (Desai. *et al , Tetrahedron Letters,* **34**(48). 7685 (1993)) in chloroform are added 1 equivalent of 6-amino-3-(dimethyl)amino-1,2,3 4-tetrahydro-9H-carbazole and 2-3 equivalents of the carboxylic acid The reaction is agitated until the reaction is complete heat may be applied if necessary The resin is removed by filtration and the product isolated by evaporation of solvent This procedure is illustrated by Examples 90-108

EXAMPLE B-90

6-(2-thienoyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

Beginning with 8 7 mg (0 038 mMol) 6-amino-3-(dimethyl)amino-1,2,3,4-tetrahydro-9H-carbazole and 11 0 mg (0 086 mMol) thiophene-2-carboxylic acid. 6 0 mg (47%) of the title compound were recovered as a beige solid
MS(m/e) 339(M^+)

EXAMPLE B-91

6-(5-methylfur-3-oyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

Beginning with 8 7 mg (0 038 mMol) 6-amino-3-(dimethyl)amino-1,2,3,4-tetrahydro-9H-carbazole and 10 0 mg (0 090 mMol) 5-methylfuran-3-carboxylic acid. 7 9 mg (62%) of the title compound were recovered as a beige solid
MS(m/e) 337(M^+)

EXAMPLE B-92

6-(2-methylfur-3-oyl)amino-3-(dimethyl)amino-1,2 3,4-tetrahydro-9H-carbazole

Beginning with 8 7 mg (0 038 mMol) 6-amino-3-(dimethyl)amino-1,2 3 4-tetrahydro-9H-carbazole and 11 mg (0 087 mMol) 2-methylfuran-3-carboxylic acid 12 7 mg (99%) of the title compound were recovered as a beige solid
MS(m/e) 337(M^+)

EXAMPLE B-93

6-(5-methylfur-2-oyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

Beginning with 8 7 mg (0 038 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 11 0 mg (0 084 mMol) 5-methylfuran-2-carboxylic acid 6 8 mg (53%) of the title compound were recovered as a beige solid
MS(m/e) 337(M^+)

EXAMPLE B-94

6-(3-methylthien-2-oyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

Beginning with 8 7 mg (0 038 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 12 mg (0 084 mMol) 3-methylthiophene-2-carboxylic acid, the title compound was recovered as a beige solid

EXAMPLE B-95

6-(4-methoxythien-3-oyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

Beginning with 8 7 mg (0 038 mMol) 6-amino-3-(dimethyl)amino-1,2 3 4-tetrahydro-9H-carbazole and 13 0 mg (0 082 mMol) 5-methoxythiophene-2-carboxylic acid 9 6 mg (69%) of the title compound were recovered as a beige solid
MS(m/e) 369(M^+)

EXAMPLE B-96

6-(2,6-dichlorobenzoyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

Beginning with 8 7 mg (0 038 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 18 0 mg (0 086 mMol) 2 6-dichlorobenzoic acid 2 4 mg (16%) of the title compound were recovered as a beige solid
MS(m/e) 401(M^+)

EXAMPLE B-97

6-(3-furoyl)amino-3-(dimethyl)amino-1,2,3 4-tetrahydro-9H-carbazole

Beginning with 8 7 mg (0 038 mMol) 6-amino-3-(dimethyl)amino-1 2 3,4-tetrahydro-9H-carbazole and 10 0 mg (0 089 mMol) furan-3-carboxylic acid, 5 8 mg (47%) of the title compound were recovered as a beige solid
MS(m/e) 324(M^+)

EXAMPLE B-98

6-(3-thienoyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

Beginning with 8 7 mg (0 038 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 11 0 mg (0 086 mMol) thiophene-3-carboxylic acid 6 8 mg (53%) of the title compound were recovered as a beige solid
MS(m/e) 339(M^+)

EXAMPLE B-99

6-(4-methansulfonylbenzoyl)amino-3-(dimethyl)amino-1 2,3 4-tetrahydro-9H-carbazole

Beginning with 8 7 mg (0 038 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 17 0 mg (0 085 mMol) 4-methanesulfonylbenzoic acid 2 0 mg (13%) of the title compound were recovered as a beige solid
MS(m/e) 411(M^+)

EXAMPLE B-100

6-(4-pyridinecarbonyl)amino-3-(dimethyl)amino-1,2,3 4-tetrahydro-9H-carbazole

Beginning with 9 2 mg (0 040 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 12 5 mg (0 101 mMol) 4-pyridinecarboxylic acid 5 0 mg (37%) of the title compound were recovered as a beige solid
MS(m/e) 334(M^+)

EXAMPLE B-101

6-(3-pyridinecarbonyl)amino-3-(dimethyl)amino-1 2,3 4-tetrahydro-9H-carbazole

Beginning with 9 2 mg (0 040 mMol) 6-amino-3-(dimethyl)amino-1 2,3 4-tetrahydro-9H-carbazole and 12 5 mg (0 101 mMol) 3-pyridinecarboxylic acid 7 2 mg (54%) of the title compound were recovered as a beige solid
MS(m/e) 334(M^+)

EXAMPLE B-102

6-(2-chloro-3-pyridinecarbonyl)amino-3-(dimethyl)amino-1 2 3,4-tetrahydro-9H-carbazole

Beginning with 9 2 mg (0 040 mMol) 6-amino-3-(dimethyl)amino-1,2,3,4-tetrahydro-9H-carbazole and 15 9 mg (0 101 mMol) 2-chloro-3-pyridinecarboxylic acid the title compound was recovered as a white solid

EXAMPLE B-103

6-(6-chloro-3-pyridinecarbonyl)amino-3-(dimethyl)amino-1,2,3 4-tetrahydro-9H-carbazole

Beginning with 9 2 mg (0 040 mMol) 6-amino-3-(dimethyl)amino-1,2,3,4-tetrahydro-9H-carbazole and 4 9 mg (0 101 mMol) 6-chloro-3-pyridinecarboxylic acid 4 9 mg (31%) of the title compound were recovered as a brown solid
MS(m/e) 369(M^+)

EXAMPLE B-104

6-(cyclopentanoyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

Beginning with 9 2 mg (0 040 mMol) 6-amino-3-(dimethyl)amino-1 2,3,4-tetrahydro-9H-carbazole and 11 6 mg (0 101 mMol) cyclopentanecarboxylic acid. 7 5 mg (53%) of the title compound were recovered as a light beige solid
MS(m/e) 326(M^+)

EXAMPLE B-105

6-(4-nitrobenzoyl)amino-3-(dimethyl)amino-1,2,3,4-tetrahydro-9H-carbazole

Beginning with 9 2 mg (0 040 mMol) 6-amino-3-(dimethyl)amino-1 2,3,4-tetrahydro-9H-carbazole and 16 9 mg (0 101 mMol) 4-nitrobenzoic acid. 1 2 mg (8%) of the title compound were recovered as a dark brown solid
MS(m/e) 379(M^+)

EXAMPLE B-106

6-(4-trifluoromethylbenzoyl)amino-3-(dimethyl)amino-1 2,3 4-tetrahydro-9H-carbazole

Beginning with 9 2 mg (0 040 mMol) 6-amino-3-(dimethyl)amino-1,2,3 4-tetrahydro-9H-carbazole and 19 2 mg (0 101 mMol) 4-trifluoromethylbenzoic acid, 5 7 mg (35%) of the title compound were recovered as a beige solid
MS(m/e) 401(M^+)

EXAMPLE B-107

6-(4-cyanobenzoyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

Beginning with 9 2 mg (0 040 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 14 9 mg (0 101 mMol) 4-cyanobenzoic acid 6 7 mg (47%) of the title compound were recovered as a beige solid
MS(m/e) 358(M^+)

EXAMPLE B-108

6-(4-acetylbenzoyl)amino-3-(dimethyl)amino-1 2 3.4-tetrahydro-9H-carbazole

Beginning with 9 2 mg (0 040 mMol) 6-amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole and 16 6 mg (0 101 mMol) 4-acetylbenzoic acid 7 8 mg (52%) of the title compound were recovered as a beige solid
MS(m/e) 375(M^+)

EXAMPLE B-109

6-(dimethylsulfonyl)amino-3-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole hydrochloride

To a solution of 0 197 gm (0 86 mMol) 6-amino-3-(dimethyl)amino-1.2 3 4-tetrahydro-9H-carbazole in 8 mL dichloromethane at 0°C were added 0 14 mL (6 18 mMol) pyridine followed by 0 14 mL (6 51 mMol) dimethylsulfamoyl chloride The reaction mixture was stirred at 0°C for 2 hours and was then allowed to warm to room temperature over 2 hours After storage at 0°C for 18 hours the reaction mixture was partitioned between 2N sodium hydroxide and 8% methanol in dichloromethane The phases were separated and the aqueous phase was extracted several times with 8% methanol in dichloromethane The organic phases were combined, dried over sodium sulfate and concentrated under reduced pressure The residue was subjected to silica gel chromatography eluting with dichloromethane containing 15% methanol and 2% ammonium hydroxide Fractions containing product were combined and concentrated under reduced pressure to give 0 20 gm (69%) of 6-(dimethylsulfonyl)amino-3-(dimethyl)amino-1 2.3 4-tetrahydro-9H-carbazole The corresponding hydrochloride salt was prepared to give the title compound which crystallized from ethanol/diethyl ether
m p =217-219°C
Exact Mass Calculated for $C_{16}H_{25}N_4O_2S$ Theory 337 1698 Found 337 1688

EXAMPLE B-110

(R)- and (S)-N-((R)-(+)-α-methyl-(4-nitrophenyl)ethyl)-6-bromo-2-amino-1 2 3 4-tetrahydro-9H-carbazole

Reductive Amination

To a solution of 20 0 gm (100 9 mMol) 1 4-cyclohexanedione mono-(2 2-dimethyl)propane-1 3-diol monoketal in 250 mL methanol were added 35 0 gm (172 7 mMol) R-(+)-α-methyl-(4-nitrophenyl)ethylamine hydrochloride, 25 0 gm (398 mMol) sodium cyanoborohydride and 10 mL acetic acid The reaction mixture was allowed to stir for 18 hours at room temperature To the reaction mixture were then added an additional charge of 25 0 gm (398 mMol) sodium cyanoborohydride and the reaction mixture stirred for an additional 18 hours at room temperature The reaction mixture was then diluted with dilute aqueous tartaric acid and the solution exhaustively extracted with dichloromethane The remainining aqueous phase was made basic with aqueous sodium hydroxide and extracted well with dichloromethane These dichloromethane extracts were combined dried over sodium sulfate and concentrated under reduced pressure to give 33 7 gm (96%) of N-((R)-(+)-α-methyl-(4-nitrophenyl)ethyl)-4-aminocyclohexanone 2.2-dimethylpropane-1 2-diol ketal as a brownish yellow oil
MS(m/e) 348(M^+)

Ketal Deprotection

A solution of 33 42 gm (95 91 mMol) N-((R)-(+)-α-methyl-(4-nitrophenyl)ethyl)-4-aminocyclohexanone 2 2-dimethylpropane-1 2-diol ketal in 250 mL 98% formic acid was heated to 40°C for 66 hours The reaction mixture was concentrated under reduced pressure to a volume of about 50 mL and was then treated with aqueous potassium carbonate The basic aqueous mixture was extracted well with dichloromethane These organic phases were combined dried

over sodium sulfate and concentrated under reduced pressure to give 22 36 gm (89%) N-((R)-(+)-α-methyl-(4-nitrophenyl)ethyl)-4-aminocyclohexanone as a brown oil

Preparation B-of henylhydrazone

To a solution of 22 3 gm (85 01 mMol) N-((R)-(+)-α-methyl-(4-nitrophenyl)ethyl)-4-aminocyclohexanone in 375 mL ethanol were added 19 0 gm (85 0 mMol) 4-bromophenylhydrazine hydrochloride and 6 73 gm (85 1 mMol) pyridine The reaction mixture was heated to 80°C for 48 hours The reaction mixture was cooled to room temperature and concentrated under reduced pressure The residue was dissolved in dichloromethane and the organic solution was washed sequentially with aqueous potassium carbonate and saturated aqueous sodium chloride The remaining organics were dried over sodium sulfate and concentrated under reduced pressure to give 31 66 gm (86%) N-((R)-(+)-α-methyl-(4-nitrophenyl)-ethyl)-4-aminocyclohexanone 4-bromophenylhydrazone as a brown solid

Fischer indole reaction

A solution of 31 66 gm (73 4 mMol) N-((R)-(+)-α-methyl-(4-nitrophenyl)ethyl)-4-aminocyclohexanone 4-bromophenyl-hydrazone in 500 mL 3 7 M ethanolic hydrogen chloride was stirred at reflux for 18 hours The reaction mixture was cooled to room temperature and was then concentrated unde reduced pressure The residue was partitioned between 1 N sodium hydroxide and dichloromethane The aqueous phase was extracted well with dichloromethane The organic phases were combined, dried over sodium sulfate and concentrated under reduced pressure The residue was subjected to silica gel chromatography eluting with 5% methanol in dichloromethane which contained 1% ammonium hydroxide

(S)-(-)-N-((R)-(+)-α-methyl-(4-nitrophenyl)ethyl)-6-bromo-3-amino-1,2 3 4-tetrahydro-9H-carbazole

The fastest eluting diastereomer was recovered as 9 47 gm (31%) of a reddish-brown oil
MS(m/e) 415(M^+)
IR($CHCl_3$) 3471, 2970 2926 2845, 1522, 1471, 1348. 857 cm^{-1}
$[\alpha]D^{20}$ (c=10 methanol) -122 3°
Calculated for $C_{20}H_{20}N_3O_2Br$ Theory C, 57 78. H 4 87 N, 10 14 Found C, 58 23 H. 5 03 N, 10 12

(R)-(+)-N-((R)-(+)-α-methyl-(4-nitrophenyl)ethyl)-6-bromo-3-amino-1 2,3,4-tetrahydro-9H-carbazole

The slower eluting diastereomer was recovered as 8 13 gm (27%) of pale green crystals
MS(m/e) 415(M^+)
IR($CHCl_3$) 3471, 3012 2970 2952, 2846, 1522, 1471, 1348. 857 cm^{-1}
$[\alpha]_D^{20}$(c=10 methanol) +337 9°
Calculated for $C_{20}H_{20}N_3O_2Br$ Theory C, 57 78 H 4 87 N 10 14 Found C 58 26 H 5 03 N 9 93
X-Ray crystallography determined that the slower eluting diastereomer was of the S,R absolute configuration

EXAMPLE B-111

(R)-(+)-6-bromo-2-(dimethyl)amino-1,2,3,4-tetrahydro-9H-carbazole hydroiodide

Quaternization

To a solution of 5 00 gm (12 1 mMol) (R)-(+)-N-((R)-(+)-α-methyl-(4-nitrophenyl)ethyl)-6-bromo-2-amino-1 2 3,4-tetrahydro-9H-carbazole in 150 mL acetonitrile were added 10 0 mL iodomethane followed by 5 0 gm potassium carbonate The mixture was stirred for 2 days at room temperature and then for 18 hours at reflux The reaction mixture was then cooled to room temperature and the resulting yellow precipitate filtered, washed with methanol and dried under reduced pressure to give 3 65 gm (53%) (R)-(+)-N,N-dimethyl-N-((R)-(+)-α-methyl-(4-nitrophenyl)ethyl)-6-bromo-2-amino-1,2,3 4-tetrahydro-9H-carbazole iodide as a yellow solid
Calculated for C22H25N302BrI Theory C 46 34 H. 4 42 N, 7 37 Found C, 46 22. H, 4 41 N 7 30

Hydrogenolysis

A mixture of 0 70 gm (1 23 mMol) (R)-(+)-N N-dimethyl-N-((R)-(+)-α-methyl-(4-nitrophenyl)ethyl)-6-bromo-2-amino-1 2 3,4-tetrahydro-9H-carbazole iodide and 0 20 gm sulfided platinum on carbon in 150 mL methanol were hydro-

genated at room temperature for 18 hours at an initial hydrogen pressure of 40 p s i The reaction mixture was then degassed and warmed to effect methanolysis The reaction mixture was filtered and concentrated under reduced pressure to give 0 471 gm (91%) of the title compound as a light yellow solid
m p =252°C
MS(m/e) 293(M^+)
IR(KBr) 3271 3016 2924 2842 2737 2709 1469 1460 1435 1302 793 cm^{-1}
$[\alpha]_D^{20}$(c=10 methanol) +54 7°
Calculated for $C_{14}H_{18}N_2Br$I Theory C 39 93 H 4 31 N 6 65 Found C 39 87 H 4 19 N 6 38

EXAMPLE B-112

Resolution of Racemic 6-bromo-2-(dimethyl)amino-1 2 3,4-tetrahydro-9H-carbazole

To a solution of 5 0 gm (17 06 mMol) 6-bromo-2-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole in 200 mL of warm ethyl acetate was added a solution of 6 59 gm (17 06 mMol) di-p-toluoyl-D-tartaric acid in 100 mL ethyl acetate with mixing After standing for 4 hours, the resulting precipitate was filtered and dried to give 12 0 gm of the salt A suspension of 1 0 gm of this solid was heated to boiling in 10 mL of methanol This mixture was then cooled to room temperature and allowed to stand for 18 hours The remaining solid was filtered and dried to give 0 65 gm This solid was again suspended in 10 mL boiling methanol and allowed to cool and stand for 18 hours to give 0 52 gm of solid after filtration and vacuum drying This solid was partitioned between dichloromethane and dilute aqueous sodium hydroxide The phases were separated and the organics were washed with saturated aqueous sodium chloride dried over sodium sulfate and concentrated under reduced pressure The residue was dissolved in 7 mL of toluene and allowed to stand at room temperature for 18 hours The solution was filtered to remove the solid which had formed and the filtrate was concentrated under reduced pressure to give 0 133 gm of an oil which gradually crystallized
m p =131-3°C
$[\alpha]_D^{20}$(c=10, methanol) -83°
The two methanol filtrates were combined and concentrated under reduced pressure to give 0 33 gm of a glass The glass was treated as described above to give 0 121 gm of an oil which gradually crystallized
m p =131-4°C
$[\alpha]_D^{20}$(c=10 methanol) +78°

EXAMPLE B-113

(R)-(+)-6-(t-butyloxycarbonyl)amino-2-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

Beginning with (R)-(+)-6-bromo-2-(dimethyl)amino-1 2 3,4-tetrahydro-9H-carbazole the title compound was prepared by the procedure described in Preparation B-III
$[\alpha]_D^{20}$(c=10 methanol) +73°

EXAMPLE B-114

(S)-(-)-6-(t-butyloxycarbonyl)amino-2-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole

Beginning with (S)-(-)-6-bromo-2-(dimethyl)amino-1 2 3,4-tetrahydro-9H-carbazole the title compound was prepared by the procedure described in Preparation B-III
$[\alpha]_D^{20}$(c=10 methanol) -72°

EXAMPLE B-115

(R)-(+)-6-(4-fluorobenzoyl)amino-2-(dimethyl)amino-1 2 3,4-tetrahydro-9H-carbazole

Beginning with (R)-(+)-6-bromo-2-(dimethyl)amino-1 2 3 4-tetrahydro-9H-carbazole, the title compound was prepared by the procedure described in EXAMPLE B-52
$[\alpha]_D^{20}$(c=10, methanol) +75°

EXAMPLE B-116

(S)-(-)-6-(4-fluorobenzoyl)amino-2-(dimethyl)amino-1 2 3.4-tetrahydro-9H-carbazole

Beginning with (S)-(-)-6-bromo-2-(dimethyl)amino-1 2 3,4-tetrahydro-9H-carbazole the title compound was prepared by the procedure described in EXAMPLE B-52
$[\alpha]_D^{20}$(c=10 methanol) -70°

The above groups of compounds are only illustrative of the serotonin 5-HT_{1F} receptor agonists which are currently under development This listing of groups of compounds is not meant to be comprehensive the method of the present invention may employ any serotonin 5-HT_{1F} receptor agonist and is not limited to any particular class of compound

While all compounds exhibiting serotonin 5-HT_{1F} receptor agonist activity are useful for the method of the present invention compounds which are selective for the serotonin 5-HT_{1F} receptor relative to other receptors are preferred Particularly preferred serotonin 5-HT_{1F} receptor agonists are those of Formula IV *supra* Especially preferred is the compound of Formula IV which is N-(4-fluorobenzoyl)-5-amino-3-(1-methylpiperidin-4-yl)-1H-indole It is also preferred that the mammal treated by the method of the present invention is a human

To demonstrate the use of the compounds of this invention in the treatment of migraine their ability to bind to the 5-HT_{1F} receptor subtype was determined The ability of the compounds of this invention to bind to the 5-HT_{1F} receptor subtype was measured essentially as described in N Adham. *et al*, *Proceedings of the National Academy of Sciences (USA)*, **90**. 408-412 (1993)

Membrane Preparation

Membranes were prepared from transfected Ltk- cells which were grown to 100% confluency The cells were washed twice with phosphate-buffered saline. scraped from the culture dishes into 5 mL of ice-cold phosphate-buffered saline and centrifuged at 200 x g for 5 minutes at 4°C The pellet was resuspended in 2 5 mL of ice-cold Tris buffer (20 mM Tris HCl. pH=7 4 at 23°C. 5 mM EDTA) and homogenized with a Wheaton tissue grinder The lysate was subsequently centrifuged at 200 x g for 5 minutes at 4°C to pellet large fragments which were discarded The supernatant was collected and centrifuged at 40.000 x g for 20 minutes at 4°C The pellet resulting from this centrifugation was washed once in ice-cold Tris wash buffer and resuspended in a final buffer containing 50 mM Tris HCl and 0 5 mM EDTA. pH=7 4 at 23°C Membrane preparations were kept on ice and utilized within two hours for the radioligand binding assays Protein concentrations were determined by the method of Bradford *(Anal Biochem*, **72**. 248-254 (1976))

Radioligand Binding

[^{3}H-5-HT] binding was performed using slight modifications of the 5-HT_{1D} assay conditions reported by Herrick-Davis and Titeler (J *Neurochem*, **50**, 1624-1631 (1988)) with the omission of masking ligands Radioligand binding studies were achieved at 37°C in a total volume of 250 µL of buffer (50 mM Tris, 10 mM $MgCl_2$, 0 2 mM EDTA 10 µM pargyline, 0 1% ascorbate pH=7 4 at 37°C) in 96 well microtiter plates Saturation studies were conducted using [^{3}H] 5-HT at 12 different concentrations ranging from 0 5 nM to 100 nM Displacement studies were performed using 4 5-5 5 nM [^{3}H]5-HT The binding profile of drugs in competition experiments was accomplished using 10-12 concentrations of compound Incubation times were 30 minutes for both saturation and displacement studies based upon initial investigations which determined equilibrium binding conditions Nonspecific binding was defined in the presence of 10 µM 5-HT Binding was initiated by the addition of 50 µL membrane homogenates (10-20 µg) The reaction was terminated by rapid filtration through presoaked (0 5% poylethyleneimine) filters using 48R Cell Brandel Harvester (Gaithersburg MD) Subsequently, filters were washed for 5 seconds with ice cold buffer (50 mM Tris HCl. pH=7 4 at 4°C), dried and placed into vials containing 2 5 mL Readi-Safe (Beckman Fullerton CA) and radioactivity was measured using a Beckman LS 5000TA liquid scintillation counter The efficiency of counting of [^{3}H]5-HT averaged between 45-50% Binding data was analyzed by computer-assisted nonlinear regression analysis (Accufit and Accucomp Lunden Software, Chagrin Falls, OH) IC_{50} values were converted to Ki values using the Cheng-Prusoff equation *(Biochem Pharmacol*, **22**. 3099-3108 (1973) All experiments were performed in triplicate All of the compounds of the invention exemplified exhibited an IC_{50} at the 5-HT_{1F} receptor of at least 5 µmol

As was reported by R L Weinshank. *et al*, WO93/14201 the 5-HT_{1F} receptor is functionally coupled to a G-protein as measured by the ability of serotonin and serotonergic drugs to inhibit forskolin stimulated cAMP production in NIH3T3 cells transfected with the 5-HT_{1F} receptor Adenylate cyclase activity was determined using standard techniqu s A maximal effect is achieved by serotonin An Emax is determined by dividing the inhibition of a test compound by the maximal effect and determining a percent inhibition (N Adham *et al supra*.. R L Weinshank. *et al*, *Proceedings of the National Academy of Sciences (USA)*, **89**,3630-3634 (1992)) and the references cited therein

Measurement of cAMP formation

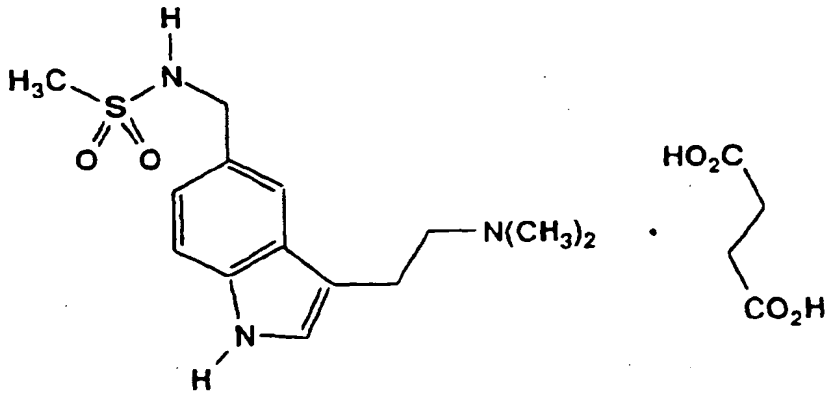
Transfected NIH3T3 cells (estimated Bmax from one point competition studies=488 fmol/mg of protein) were incubated in DMEM 5 mM theophylline 10 mM HEPES (4-[2-hydroxyethyl]-1-piperazineethanesulfonic acid) and 10 μM pargyline for 20 minutes at 37°C. 5% CO_2 Drug dose-effect curves were then conducted by adding 6 different final concentrations of drug followed immediately by the addition of forskolin (10 μM) Subsequently the cells were incubated for an additional 10 minutes at 37°C, 5% CO_2 The medium was aspirated and the reaction was stopped by the addition of 100 mM HCl To demonstrate competitive antagonism a dose-response curve for 5-HT was measured in parallel using a fixed dose of methiothepin (0 32 μM) The plates were stored at 4°C for 15 minutes and then centrifuged for 5 minutes at 500 x g to pellet cellular debris and the supernatant was aliquoted and stored at -20°C before assessment of cAMP formation by radioimmunoassay (cAMP radioimmunoassay kit Advanced Magnetics, Cambridge, MA) Radioactivity was quantified using a Packard COBRA Auto Gamma counter equipped with data reduction software

To establish that the 5-HT_{1F} receptor subtype is responsible for mediating neurogenic meningeal extravasation which leads to the pain of migraine the binding affinity of a panel of compounds to serotonin receptors was measured first using standard procedures For example, the ability of a compound to bind to the 5-HT_{1F} receptor subtype was performed as described *supra* For comparison purposes the binding affinities of compounds to the 5-$HT_{1Dα}$, 5-$HT_{1Dβ}$, 5-HT_{1E} and 5-HT_{1F} receptors were also determined as described *supra*, except that different cloned receptors were employed in place of the 5-HT_{1F} receptor clone employed therein The same panel was then tested in the cAMP assay to determine their agonist or antagonist character Finally the ability of these compounds to prevent neuronal protein extravasation, a functional assay for migraine pain was measured

The panel of compounds used in this study represents distinct structural classes of compounds which were shown to exhibit a wide range of affinities for the serotonin receptors assayed Additionally the panel compounds were shown to have a wide efficacy range in the neuronal protein extravasation assay as well The panel of compounds selected for this study are described below

Compound I

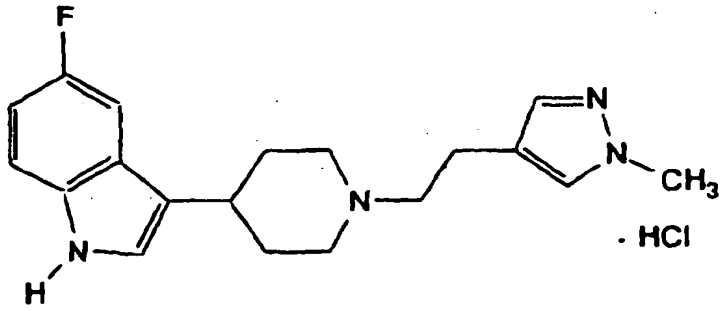
3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulfonamide butane-1 4-dioate (1 1) (Sumatriptan succinate)



Sumatriptan succinate is commercially available as Imitrex™ or may be prepared as described in United States Patent 5 037 845 issued August 6 1991 which is herein incorporated by reference

Compound II

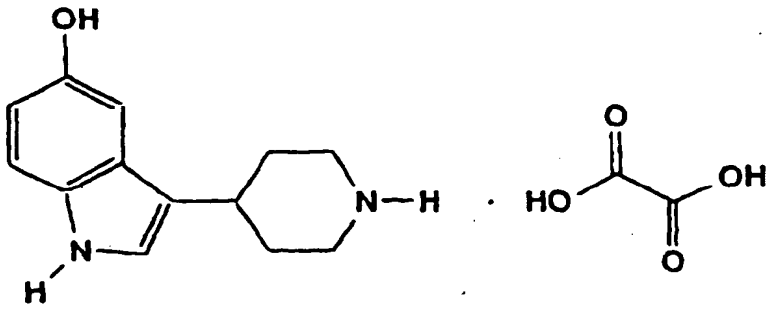
5-fluoro-3-<1-<2-<1-methyl-1H-pyrazol-4-yl>ethyl>-4-piperidinyl>-1H-indole hydrochloride



Compound II a compound useful for the method of the present invention, is described in United States Patent #5 521 196 issued May 28, 1996 which is herein incorporated by reference in its entirety

Compound III

5-hydroxy-3-(4-piperidinyl)-1H-indole oxalate



Compound III is available by the following procedure

5-benzyloxy-3-(1,2,5,6-tetrahydro-4-pyridinyl]-1H-indole

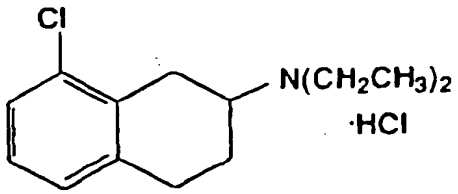
Starting with 5 0 gm (22 mMol) 5-benzyloxyindole and 6 88 gm (45 mMol) 4-piperidone•HCl•H_2O 6 53 gm (97 6%) of 5-benzyloxy-3-[1.2 5.6-tetrahydro-4-pyridinyl]-1H-indole were recovered as a light yellow solid by the procedure described in Preparation I The material was used in the subsequent step without further purification

Hydrogenation/Hydrogenolysis

To a solution of 1 23 gm (4 mMol) 5-benzyloxy-3-[1,2,5,6-tetrahydro-4-pyridinyl]-1H-indole in 50 mL 1:1 tetrahydrofuran ethanol were added 0 3 gm 5% palladium on carbon and the reaction mixture hydrogenated at ambient temperature for 18 hours with an initial hydrogen pressure of 60 p s i The reaction mixture was then filtered through a celite pad and the filtrate concentrated under reduced pressure The residue was converted to the oxalate salt and 0 98 gm (80 0%) of Compound III were recovered as a brown foam
m p =67°C
MS(m/e) 216(M^+)
Calculated for $C_{13}H_{16}N_2O•C_2H_2O_4$ Theory C, 58 81 H, 5 92 N 9 14 Found C, 58 70, H 5 95 N, 9 39

Compound IV

8-chloro-2-diethylamino-1 2 3 4-tetrahydronaphthalene hydrochloride



Compound IV is available by the following procedure

8-chloro-2-tetralone

A mixture of 30 0 gm (0 176 mole) of -chlorophenylacetic acid and 40 0 mL of thionyl chloride was stirred at ambient temperature for 18 hours The volatiles were then removed in vacuo to give 32 76 gm (99 0 %) of o-chlorophenylacetyl chloride as a transparent pale yellow mobile liquid
NMR($CDCl_3$) 7 5-7 1 (m 4H) 4 2 (s 2H)

To a slurry of 46 5 gm (0 348 mole) $AlCl_3$ in 400 mL dichloromethane at -78°C was added a solution of 32 76 gm (0 174 mole) of the previously prepared o-chlorophenylacetyl chloride in 100 mL dichloromethane dropwise over 1 hour The dry ice/acetone bath then was replaced with an ice/water bath and ethylene was bubbled into the reaction mixture during which time the temperature rose to 15°C The ethylene addition was discontinued at the end of the exotherm and the reaction mixture was stirred at about 5°C for 4 hours Ice was then added to the reaction mixture to destroy aluminum complexes Upon termination of the exotherm, the reaction mixture was diluted with 500 mL of water and stirred vigorously until all solids had dissolved The phases were separated and the organic phase was washed with 3x400 mL 1N hydrochloric acid and 2x400 mL saturated aqueous sodium bicarbonate The remaining organic phase was then dried over sodium sulfate and concentrated in vacuo to give a pale orange residue The residue was dissolved in 1 1 hexane diethyl ether and was poured over a flash silica column which was then eluted with 1 1 hexane diethyl ether to give a light yellow residue which was crystallized from 4 1 hexane diethyl ether to give 10 55 gm of the title compound
NMR($CDCl_3$) 7 5-7 2 (m 3H) 3 7 (s 2H) 3 3-3 0 (t J=7 Hz 2H) 2 8-2 4 (t J=7 Hz 2H)
MS 180(60) 165(9), 138(100), 117(52) 115(50) 103(48), 89(20), 76(25), 74(18), 63(30), 57(9) 52(28) 51(20), 42 (6), 39(32)
IR(nujol mull) 2950 cm^{-1} 2927 cm^{-1} 1708 cm^{-1} 1464 cm^{-1} 1450 cm^{-1} 1169 cm^{-1}, 1141 cm^{-1}

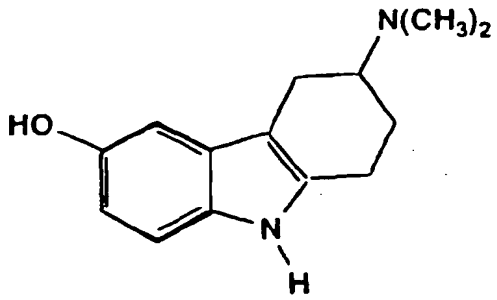
Reductive Amination

To a solution of 0 5 gm (2 78 mMol) 8-chloro-2-tetralone in 25 mL cyclohexane were added 1 4 mL (13 9 mMol) diethylamine followed by 0 1 gm p-toluenesulfonic acid monohydrate The reaction mixture was then heated at reflux with constant water removal (Dean-Stark Trap) for 18 hours The reaction mixture was then cooled to ambient and the volatiles removed under reduced pressure The residue was then dissolved in 15 mL methanol to which were then added 1 5 mL acetic acid followed by the portionwise addition of 0 5 gm sodium borohydride The reaction mixture was then stirred for 1 hour at ambient .

The reaction mixture was then diluted with 20 mL 10% HCl and stirred for an additional hour The mixture was then extracted with diethyl ether and the remaining aqueous phase was poured over ice, made basic with ammonium hydroxide and extracted well with dichloromethane These extracts were combined dried over sodium sulfate and concentrated under reduced pressure The residue was redissolved in dichloromethane and subjected to chromatography over basic alumina, eluting with dichloromethane Fractions shown to contain product were combined and concentrated under reduced pressure The residual oil was dissolved in diethyl ether and the solution saturated with hydrogen chloride The viscous residue was crystallized from acetone/diethyl ether to give 0 20 gm (23 2 %) of Compound IV as colorless crystals
m p =158-159°C
MS(m/e) 273
Calculated for $C_{14}H_{21}NCl{\cdot}HCl$ Theory C 61 32 H 7 72 N 5 11 Found C 61 62 H, 7 94 N, 5 03

Compound V

6-hydroxy-3-dimethylamino-1 2 3 4-tetrahydrocarbazole



Compound V is available by the following procedure

4-dimethylamino-1-cyclohexanone ethylene ketal

To a solution of 5 0 gm (32 mMol) 1,4-cyclohexanedione *mono*-ethylene ketal and 10 80 gm (240 mMol) dimethylamine were added 2 0 mL acetic acid and the mixture was stirred at 0°C for 1 5 hours To this solution were then added 3 62 gm (58 mMol) sodium cyanoborohydride and the reaction stirred for an additional hour at ambient The pH of the reaction mixture was adjusted to ~7 with 16 mL acetic acid and stirred 18 hours at ambient The volatiles were removed under reduced pressure and the residue dissolved in cold 5% tartaric acid solution and then the aqueous phase was made basic with 5N sodium hydroxide This aqueous phase was extracted well with dichloromethane These organic extracts were combined and concentrated under reduced pressure to give 5 04 gm (85%) of the title compound as an oil

4-dimethylamino-1-cyclohexanone

4 96 gm (26 8 mMol) 4-dimethylamino-l-cyclohexanone ethylene ketal were dissolved in 50 mL formic acid and the solution stirred at reflux for 18 hours The reaction mixture was then cooled to ambient and the volatiles removed under reduced pressure to give 3 78 gm (100%) of the title compound

6-benzyloxy-3-dimethylamino-1 2 3 4-tetrahydrocarbazole

To a solution of 3 78 gm (26 8 mMol) 4-dimethylamino-1-cyclohexanone and 6 69 gm (26 8 mMol) 4-benzyloxyphenylhydrazine hydrochloride in 50 mL ethanol were added 2 17 mL (26 8 mMol) pyridine To this solution were added 5x10 mL portions of water and the reaction mixture then stored at 0°C for 18 hours The reaction mixture was then diluted with an additional 50 mL of water and the mixture extracted well with dichloromethane The combined organic extracts were dried over sodium sulfate and the volatiles removed under reduced pressure The residual oil was subjected to flash silica gel chromatography, eluting with 9 1 chloroform methanol Fractions shown to contain the desired product were combined and concentrated under reduced pressure to give 2 14 gm (24 9%) of the title compound

Hydrogenolysis

To a solution of 2 14 gm (6 7 mMol) 6-benzyloxy-3-dimethylamino-1.2 3,4-tetrahydrocarbazole in 50 mL ethanol were added 0 20 gm 10% palladium on carbon and the reaction mixture was hydrogenated at ambient temperature with an initial hydrogen pressure of 40 p s i After 5 hours an additional charge of 0 20 gm 10% palladium on carbon were added and the reaction mixture repressurized with hydrogen to 40 p s i for 4 hours The reaction mixture was then filtered through a pad of celite and the filtrate concentrated under reduced pressure The residue was subjected to Florisil chromatography, eluting with 9 1 chloroform methanol Fractions shown to contain the desired compound were combined and concentrated under reduced pressure The residue was again subjected to Florisil chromatography, eluting with a gradient consisting of chloroform containing 2-10% methanol Fractions shown to contain product were combined and concetnrated under reduced pressure to give Compound V as a crystalline solid
MS(m/e) 230(M^+)

Calculated for $C_{14}H_{18}N_2O$ Theory C 73 01 H 7 88 N 12 16 Found C 72 75 H 7 83 N 11 97

Binding Assays

The binding affinities of compounds for various serotonin receptors were determined essentially as described above except that different cloned receptors are employed in place of the 5-HT_{1F} receptor clone employed therein The results of these binding experiments are summarized in Table II

TABLE II

BINDING TO SERCTONIN (5-HT_1) RECEPTOR SUBTYPES (K_i nM)				
Compound	**5-$HT_{1D\alpha}$**	**5-$HT_{1D\beta}$**	**5-HT_{1E}**	**5-HT_{1F}**
I	4 8	9 6	2520 0	25 7
II	21 7	53 6	50 3	2 5
III	163 2	196 5	3 9	22 0
IV	13 5	145 3	813 0	129 2
V	791 0	1583 0	73 6	10 3

cAMP Formation

All of the compounds of the panel were tested in the cAMP formation assay described *supra* and all were found to be agonists of the 5-HT_{1F} receptor

Protein Extravasation

Harlan Sprague-Dawley rats (250-350 g) or guinea pigs from Charles River Laboratories (250-350 g) were anesthetized with sodium pentobarbital intraperitoneally (65 mg/kg or 45 mg/kg respectively) and placed in a stereotaxic frame (David Kopf Instruments) with the incisor bar set at -3 5 mm for rats or -4 0 mm for guinea pigs Following a midline sagital scalp incision, two pairs of bilateral holes were drilled through the skull (6 mm posteriorly, 2 0 and 4 0 mm laterally in rats 4 mm posteriorly and 3 2 and 5 2 mm laterally in guinea pigs, all coordinates referenced to bregma) Pairs of stainless steel stimulating electrodes, insulated except at the tips (Rhodes Medical Systems, Inc) were lowered through the holes in both hemispheres to a depth of 9 mm (rats) or 10 5 mm (guinea pigs) from dura

The femoral vein was exposed and a dose of the test compound was injected intravenously (1 mL/kg) Approximately 7 minutes later, a 50 mg/kg dose of Evans Blue, a fluorescent dye was also injected intravenously The Evans Blue complexed with proteins in the blood and functioned as a marker for protein extravasation Exactly 10 minutes post-injection of the test compound, the left trigeminal ganglion was stimulated for 3 minutes at a current intensity of 1 0 mA (5 Hz, 4 msec duration) with a Model 273 potentiostat/ galvanostat (EG&G Princeton Applied Research)

Fifteen minutes following stimulation the animals were killed by exsanguination with 40 mL of saline The top of the skull was removed to facilitate the collection of the dural membranes The membrane samples were removed from both hemispheres rinsed with water and spread flat on microscopic slides Once dried the tissues were coverslipped with a 70% glycerol/water solution

A fluorescence microscope (Zeiss) equipped with a grating monochromator and a spectrophotometer was used to quantify the amount of Evans Blue dye in each sample An excitation wavelength of approximately 535 nm was utilized and the emission intensity at 600 nm was determined The microscope was equipped with a motorized stage and also interfaced with a personal computer This facilitated the computer-controlled movement of the stage with fluorescence measurements at 25 points (500 µm steps) on each dural sample The mean and standard deviation of the measurements was determined by the computer

The extravasation induced by the electrical stimulation of the trigeminal ganglion was an ipsilateral effect (i e occurs only on the side of the dura in which the trigeminal ganglion was stimulated) This allows the other (unstimulated) half of the dura to be used as a control The ratio of the amount of extravasation in the dura from the stimulated side compared to the unstimulated side dura was calculated Saline controls yielded a ratio of approximately 2 0 in rats and 1 8 in guinea pigs In contrast a compound which effectively prevented the extravasation in the dura from the stimulated side would have a ratio of approximately 1 0 A dose-response curve was generated and the dose that inhibited the extravasation by 50% (ID_{50}) was approximated This data is presented in Table III

Table III

Inhibition of Protein Extravasation (ID_{50} mMol/kg)	
Compound	**i.v. ID_{50} (mMol/kg)**
I	2.6×10^{-8}
II	8.6×10^{-10}
III	8.9×10^{-9}
IV	1.2×10^{-7}
V	8.7×10^{-9}

To determine the relationship of binding at various serotonin receptors to inhibition of neuronal protein extravasation, the binding affinity of all of the compounds to each of the 5-$HT_{1D\alpha}$, 5-$HT_{1D\beta}$, 5-HT_{1E} and 5-HT_{1F} receptors was plotted against their ID_{50} in the protein extravasation model. A linear regression analysis was performed on each set of data and a correlation factor R^2 calculated. The results of this analysis are summarized in Table IV.

Table IV

Correlation Factor (R^2) for Specific 5-HT_1 Subtype Binding Affinity vs Inhibition of Protein Extravasation	
5-HT_1 Subtyte	**Correlation Factor (R^2)**
5-$HT_{1D\alpha}$	0.07
5-$HT_{1D\beta}$	0.001
5-HT_{1E}	0.31
5-HT_{1F}	0.94

An ideally linear relationship would generate a correlation factor of 1.0, suggesting a cause and effect relationship between the two variables. The experimentally determined correlation factor between inhibition of neuronal protein extravasation and 5-HT_{1F} binding affinity (pKi) is 0.94. This nearly ideal dependence of the ID_{50} in the protein extravasation model on binding affinity to the 5-HT_{1F} receptor clearly demonstrates that the 5-HT_{1F} receptor mediates the inhibition of protein extravasation resulting from stimulation of the trigeminal ganglia.

Since 5-HT_{1F} agonists inhibit protein extravasation if administered prior to stimulation of the trigeminal ganglia, they may be administered prior to a migraine attack to prevent the migraine attack and the associated pain.

While it is possible to administer a compound employed in the methods of this invention directly without any formulation, the compounds are usually administered in the form of pharmaceutical compositions comprising a pharmaceutically acceptable excipient and at least one active ingredient. These compositions can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. Many of the compounds employed in the methods of this invention are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. See, e.g., REMINGTON's PHARMACEUTICAL SCIENCES, (16th ed. 1980).

In making the compositions employed in the present invention the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g., about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include lubricating agents such as talc, magnesium stearate and mineral oil, wetting agents, emulsifying and suspending agents, preserving agents such as methyl- and propylhydroxybenzoates, sweetening agents, and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the

patient by employing procedures known in the art

The compositions are preferably formulated in a unit dosage form each dosage containing from about 0 05 to about 100 mg more usually about 1 0 to about 30 mg of the active ingredient The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with a suitable pharmaceutical excipient

The active compounds are generally effective over a wide dosage range For examples. dosages per day normally fall within the range of about 0 01 to about 30 mg/kg of body weight In the treatment of adult humans the range of about 0 1 to about 15 mg/kg/day in single or divided dose is especially preferred However it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances including the condition to be treated the chosen route of administration. the actual compound or compounds administered the age. weight and response of the individual patient and the severity of the patient's symptoms and therefore the above dosage ranges are not intended to limit the scope of the invention in any way In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate while in other cases still larger doses may be employed without causing any harmful side effect provided that such larger doses are first divided into several smaller doses for administration throughout the day

Formulation Preparation 1

Hard gelatin capsules containing the following ingredients are prepared

Ingredient	Quantity (mg/capsule)
N-(4-fluorobenzoyl)-5-amino-3-(1-methylpiperidin-4-yl)-1H-indole	30 0
Starch	305 0
Magnesium stearate	5 0

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities

Formulation Preparation 2

A tablet formula is prepared using the ingredients below

Ingredient	Quantity (mg/tablet)
N-(4-fluorobenzoyl)-5-amino-3-(1-methylpiperidin-4-yl)-1H-indole	25 0
Cellulose. microcrystalline	200 0
Colloidal silicon dioxide	10 0
Stearic acid	5 0

The components are blended and compressed to form tablets each weighing 240 mg

Formulation Preparation 3

A dry powder inhaler formulation is prepared containing the following components

Ingredient	Weight %
N-(4-fluorobenzoyl)-5-amino-3-(1-methylpiperidin-4-yl)-1H-indole	5
Lactose	95

The active mixture is mixed with the lactose and the mixture is added to a dry powder inhaling appliance

Formulation Preparation 4

Tablets each containing 30 mg of active ingredient are prepared as follows

Ingredient	Quantity (mg/tablet)
N-(4-fluorobenzoyl)-5-amino-3-(1-methylpiperidin-4-yl)-1H-indole	30 0 mg
Starch	45 0 mg
Microcrystalline cellulose	35 0 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 0 mg
Sodium carboxymethyl starch	4 5 mg
Magnesium stearate	0 5 mg
Talc	1 0 mg
Total	120 mg

The active ingredient starch and cellulose are passed through a No 20 mesh U S sieve and mixed thoroughly The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U S sieve The granules so produced are dried at 50-60°C and passed through a 16 mesh U S sieve The sodium carboxymethyl starch magnesium stearate and talc previously passed through a No 30 mesh U S sieve, are then added to the granules which after mixing are compressed on a tablet machine to yield tablets each weighing 120 mg

Formulation Preparation 5

Capsules, each containing 40 mg of medicament are made as follows

Ingredient	Quantity (mg/capsule)
N-(4-fluorobenzoyl)-5-amino-3-(1-methylpiperidin-4-yl)-1H-indole	40 0 mg
Starch	109 0 mg
Magnesium stearate	1 0 mg
Total	150 0 mg

The active ingredient, cellulose starch, and magnesium stearate are blended, passed through a No 20 mesh U S sieve and filled into hard gelatin capsules in 150 mg quantities

Formulation Preparation 6

Suppositories each containing 25 mg of active ingredient are made as follows

Ingredient	Amount
N-(4-fluorobenzoyl)-5-amino-3-(1-methylpiperidin-4-yl)-1H-indole	25 mg
Saturated fatty acid glycerides to	2 000 mg

The active ingredient is passed through a No 60 mesh U S sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary The mixture is then poured into a suppository mold of nominal 2 0 g capacity and allowed to cool

Formulation Preparation 7

Suspensions, each containing 50 mg of medicament per 5 0 ml dose are made as follows

Ingredient	Amount
N-(4-fluorobenzoyl)-5-amino-3-(1-methylpiperidin-4-yl)-1H-indole	50 0 mg
Xanthan gum	4 0 mg
Sodium carboxymethyl cellulose (11%) Microcrystalline cellulose (89%)	50 0 mg
Sucrose	1 75 g
Sodium benzoate	10 0 mg

(continued)

Ingredient	Amount
Flavor and Color	q v
Purified water to	5 0 ml

The medicament, sucrose and xanthan gum are blended passed through a No 10 mesh U S sieve and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water The sodium benzoate flavor and color are diluted with some of the water and added with stirring Sufficient water is then added to produce the required volume

Formulation Preparation 8

Capsules each containing 15 mg of medicament are made as follows

Ingredient	Quantity (mg/capsule)
N-(4-fluorobenzoyl)-5-amino-3-(1-methylpiperidin-4-yl)-1H-indole	15 0 mg
Starch	407 0 mg
Magnesium stearate	3 0 mg
Total	425 0 mg

The active ingredient cellulose, starch and magnesium stearate are blended, passed through a No 20 mesh U S sieve and filled into hard gelatin capsules in 425 mg quantities

Formulation Preparation 9

An intravenous formulation may be prepared as follows

Ingredient	Quantity
N-(4-fluorobenzoyl)-5-amino-3-(1-methylpiperidin-4-yl)-1H-indole	250 0 mg
Isotonic saline	1000 ml

Formulation Preparation 10

A topical formulation may be prepared as follows

Ingredient	Quantity
N-(4-fluorobenzoyl)-5-amino-3-(1-methylpiperidin-4-yl)-1H-indole	1-10 g
Emulsifying Wax	30 g
Liquid Paraffin	20 g
White Soft Paraffin	to 100 g

The white soft paraffin is heated until molten The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved The active ingredient is added and stirring is continued until dispersed The mixture is then cooled until solid

Formulation Preparation 11

Sublingual or buccal tablets each containing 10 mg of active ingredient, may be prepared as follows

Ingredient	Quantity Per Tablet
N-(4-fluorobenzoyl)-5-amino-3-(1-methylpiperidin-4-yl)-1H-indole	10 0 mg
Glycerol	210 5 mg
Water	143 0 mg

(continued)

Ingredient	Quantity Per Tablet
Sodium Citrate	4 5 mg
Polyvinyl Alcohol	26 5 mg
Polyvinylpyrrolidone	15 5 mg
Total	410 0 mg

The glycerol. water sodium citrate polyvinyl alcohol and polyvinylpyrrolidone are admixed together by continuous stirring and maintaining the temperature at about 90°C When the polymers have gone into solution the solution is cooled to about 50-55°C and the medicament is slowly admixed The homogenous mixture is poured into forms made of an inert material to produce a drug-containing diffusion matrix having a thickness of about 2-4 mm This diffusion matrix is then cut to form individual tablets having the appropriate size

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches") Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art See, e g. U S Patent 5.023 252 issued June 11 1991, herein incorporated by reference Such patches may be constructed for continuous pulsatile. or on demand delivery of pharmaceutical agents

Indirect techniques which are generally preferred usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs or prodrugs Latentiation is generally achieved through blocking of the hydroxy, carbonyl sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier

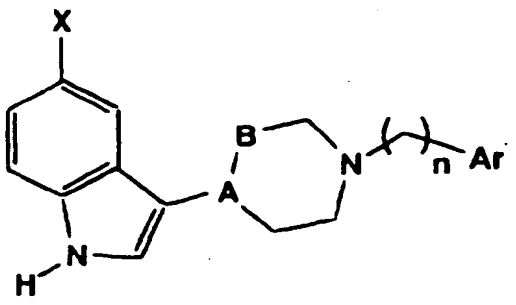
The type of formulation employed for the administration of the compounds employed in the methods of the present invention may be dictated by the particular compounds employed the type of pharmacokinetic profile desired from the route of administration and the compound, and the state of the patient

Claims

1. A method for the prevention of migraine in a mammal which comprises administering to a mammal in need thereof an effective amount of a serotonin 5-HT_{1F} agonist

2. A method of Claim 1 where the serotonin 5-HT_{1F} agonist is selective for the 5-HT_{1F} receptor relative to other receptors

3. A method as claimed in Claim 1 in which the serotonin 5-HT_{1F} agonist is a compound of Formula I

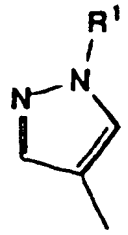


I

in which

A-B is -CH-CH_2- or -C=CH-.

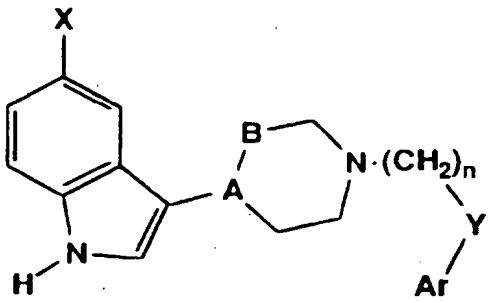
X is H halo C_1-C_4 alkoxy C_1-C_4 alkylthio C_1-C_4 alkyl benzyloxy hydroxy or carboxamide
n is 1-4
Ar is pyridinyl pyrrolyl or a structure of Formula II



II

where R^1 is H C_1-C_6 alkyl C_3-C_7 cycloalkyl C_3-C_7 cycloalkylmethyl benzyl phenyl or substituted phenyl and pharmaceutically acceptable acid addition salts thereof

4. A method as claimed in Claim 1 in which the serotonin 5-HT_{1F} agonist is a compound of Formula III



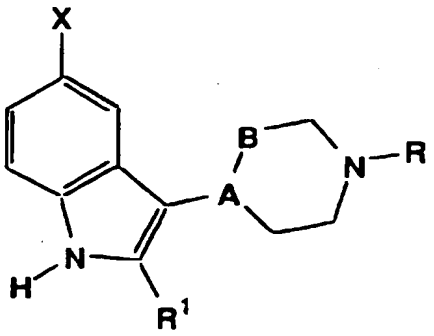
III

in which

A-B is -CH-CH_2- or -C=CH-.
X is H, halo C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkyl, benzyloxy, hydroxy or carboxamido
Y is O S or a bond
n is 1-4
Ar is 1-naphthyl, 2-naphtyl phenyl or phenyl monosubstituted with a substituent selected from the group consisting of halo C_1-C_4 alkoxy C_1-C_4 alkylthio C_1-C_4 alkyl benzyloxy hydroxy or trifluoromethyl

and pharmaceutically acceptable acid addition salts thereof

5. A method as claimed in Claim 1 in which the serotonin 5-HT_{1F} agonist is a compound of Formula IV



IV

in which

A-B is -CH-CH_2- or -C=CH-
R is H or C_1-C_6 alkyl.
R^1 is H or C_1-C_4 alkyl
X is -S-R^2 -C(O)R^3 -C(O)NR^4R^{15}, -NR^5R^6, -N$R^7SO_2R^8$,-NHC(Q)N$R^{10}R^{11}$, -NHC(O)OR^{12} or -N^{R13}C(O)R^{14}

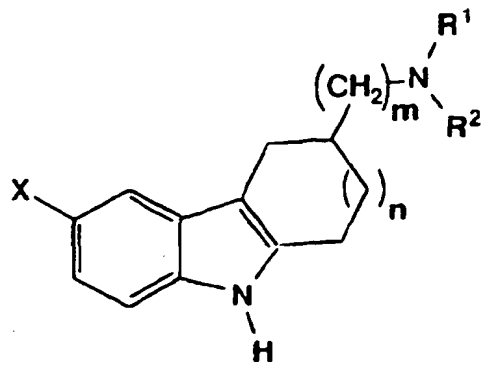
where

Q is O or S,
R^2 is phenyl substituted phenyl phenyl(C_1-C_4 alkylene), phenyl(C_1-C_4 alkylene) substituted in the phenyl ring, or pyridinyl.
R^3 is C_1-C_6 alkyl phenyl(C_1-C_4 alkylene), phenyl(C_1-C_4 alkylene) substituted in the phenyl ring, naphthyl, N-methyl-N-methoxyamino, heteroaryl, substituted heteroaryl, heteroaryl(C_1-C_4 alkyl), or substituted heteroaryl (C_1-C_4 alkyl),
R^4 is heteroaryl, substituted heteroaryl heteroaryl(C_1-C_4 alkyl), or substituted heteroaryl(C_1-C_4 alkyl),
R^4 and R^{15} taken together with the nitrogen atom form a pyrrolidine, piperidine substituted piperidine piperazine, 4-substituted piperazine, morpholine or thiomorpholine ring,
R^5 and R^6 are both trifluoromethanesulfonyl
R^7 is H or C_1-C_4 alkyl.
R^8 is C_1-C_4 alkyl phenyl, substituted phenyl, or di(C_1-C_4 alkyl)amino,
R^{10} and R^{11} are independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_8 cycloalkyl, phenyl substituted phenyl phenyl(C_1-C_4 alkylene) phenyl(C_1-C_4 alkylene) substituted in the phenyl ring, (((C_1-C_4 alkyl or C_1-C_4 alkoxycarbonyl substituted)C_1-C_4 alkyl)phenyl, C_1-C_4 alkyl α-substituted with C_1-C_4 alkoxycarbonyl or
R^{10} and R^{11} taken together with the nitrogen atom form a pyrrolidine, piperidine, piperazine, 4-substituted piperazine morpholine or thiomorpholine ring,
R^{12} is C_1-C_6 alkyl, C_3-C_6 alkenyl phenyl substituted phenyl, C_3-C_8 cycloalkyl, C_1-C_4 alkyl ω-substituted with C_1-C_4 alkoxy,
R^{13} is H or C_1-C_4 alkyl.
R^{14} is C_1-C_{10} alkyl substituted with up to three substituents selected from the group consisting of hydroxy, C_1-C_4 alkoxy, halo aryloxy, C_1-C_4 alkoxycarbonyl and heteroaryloxy, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, phenyl, substituted phenyl naphthyl, phenyl(C_1-C_4 alkylene), phenyl(C_1-C_4 alkylene) substituted on the phenyl ring, 2-phenylethylen-l-yl, diphenylmethyl, benzofused C_4-C_8 cycloalkyl, C_1-C_4 alkylene ω-substituted with C_3-C_6 cycloalkyl, or a heterocycle
R^{15} is H or C_1-C_6 alkyl

and pharmaceutically acceptable acid addition salts thereof

6. A method as claimed in Claim 5 in which the serotonin 5-HT_{1F} agonist is N-(4-fluorobenzoyl)-5-amino-3-(1-methylpiperidin-4-yl)-1H-indole, and pharmaceutically acceptable acid addition salts thereof

7. A method as claimed in Claim 1 in which the s rotonin 5-HT_{1F} agonist is a compound of Formula V



V

wherein

R^1 and R^2 are independently hydrogen C_1-C_4 alkyl, or-CH_2CH_2-Aryl where Aryl is phenyl, phenyl monosubstituted with halo, or 1-(C_1-C_6 alkyl)pyrazol-4-yl
X is -OH, -NHC(O)R^3, -NHC(Y)NHR^4, -NHC(O)OR^5, -C(O)R^6 or -$NHSO_2R^7$
R^3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, phenyl, substituted phenyl, naphthyl, (C_1-C_4 alkylene)phenyl, thienylmethyl, or a heterocycle
R^4 is C_1-C_6 alkyl, phenyl, or phenyl disubstituted with halo
R^5 is C_1-C_6 alkyl, C_2-C_6 alkenyl, benzyl, or phenyl monosubstituted with halo
R^6 is C_1-C_6 alkyl, phenyl, or phenyl monosubstituted with halo or C_1-C_4 alkoxy
R^7 is dimethylamino, phenyl, or phenyl monosubstituted with halo or C_1-C_4 alkyl
m is 0 or 1,
n is 1 or 2,
Y is S or O, and

pharaceutically acceptable acid addition salts thereof

8. A method of any of Claims 1-7 wherein the mammal is a human